Donor-Derived Cell-Free DNA Outperforms Serum Creatinine Changes for Identifying Kidney Transplant Rejection

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INTRODUCTION:

In kidney transplantation, biopsy is an invasive and expensive procedure. Serum creatinine (sCr) is commonly used to screen for rejection but is nonspecific. Donor-derived cell free DNA (dd-cfDNA) has been identified as a more specific biomarker for rejection. The performance of dd-cfDNA to detect rejection was evaluated in 107 kidney transplant patients who had clinical suspicion of rejection in the DART study[1]. When sampled at the time of biopsy, dd-cfDNA discriminated biopsy-based diagnosis of active rejection in kidney transplant patients but sCr level did not.

This study examines the performance of changes in sCr from a prior visit to discriminate active rejection. The reference standard for diagnosis of rejection or no rejection was based on the histopathology findings from a clinically-indicated biopsy performed nearest to the time of the most recent sCr measurement. A 15% to 25% increase over baseline has been used to define unstable graft function that may be attributable to rejection or other causes.[2]

METHODS:

Samples from the August 2017 data lock of the DART study were analyzed for dd-cfDNA with the analytically validated AlloSure assay[3]. Inclusion criteria were: a clinically indicated biopsy with concurrent sCr and dd-cfDNA measurements (no more than 3 days before biopsy and not after biopsy), and at least one prior sCr measurement between 4 and 60 days before the biopsy (Fig 1). Where multiple sCr values were available, the value closest to the biopsy was used. Median time interval between the current and prior sCr values was 9 days.

Performance of dd-cfDNA at the time of biopsy was compared to the performance of the change in sCr for discrimination of biopsy-based diagnosis of active antibody mediated and/or cellular rejection. A threshold of 1% was used to assess the performance of dd-cfDNA following the recommendation in Bloom et al. Performance of sCr change was assessed at three levels: 15%, 20% and 25%. Too few patients had a prior dd-cfDNA measurement so change in dd-cfDNA could not be assessed.

Fig 1. Schematic of sample selection 1

Fig 2. CONSORT diagram

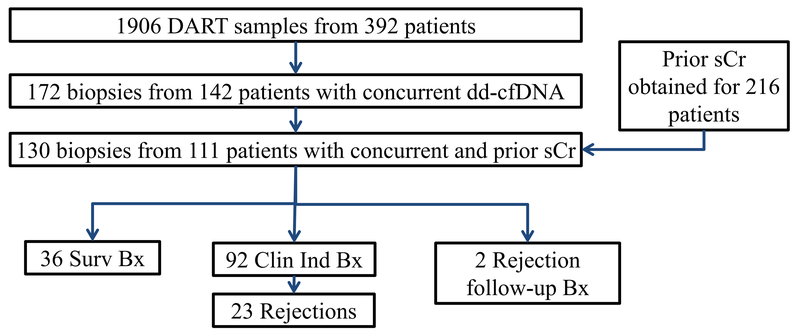

Fig 3. Serum Creatinine Change is not Impacted by Interval Length. The median interval between two sCr values is 9 days (left); low correlation (-0.25) between interval length and sCr change (right).

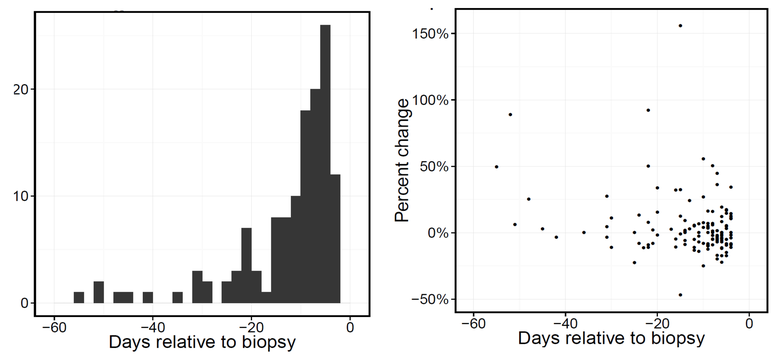

Fig 4. dd-cfDNA is significantly elevated at time of rejection compared to dd-cfDNA associated with no rejection (left). Serum creatinine changes associated with rejection are only marginally higher than those associated with no rejection and have very limited range (right). T test used for comparing sCr changes; Wilcoxon rank sum test used for dd-cfDNA changes because of skewed distribution.

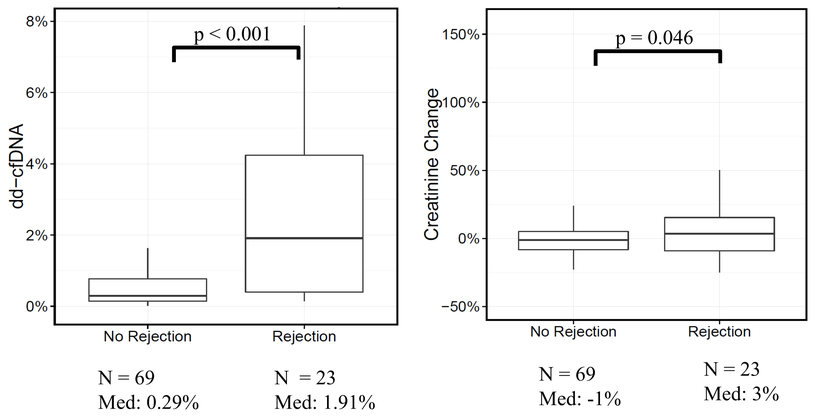

Fig 5. The threshold of serum creatinine change does not impact the sensitivity and specificity of sCr change to detect rejection

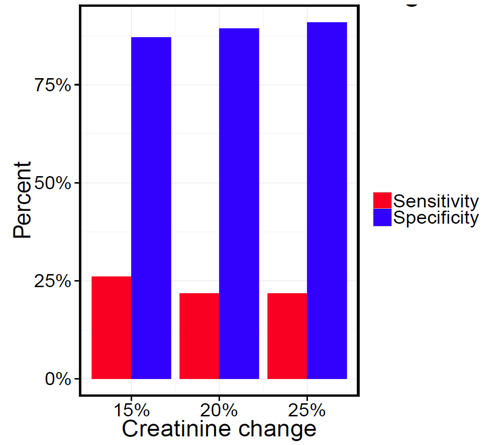

Table 1. dd-cfDNA ≥ 1% detects rejection, but serum creatinine change ≥ 25% does not. Sensitivity of dd-cfDNA is three times higher than sensitivity of sCr change and PPV is 15% higher; AUC of dd-dfDNA is 80%, whereas AUC of sCr change is not significantly different from 50%.

Biomarker	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
dd-cfDNA ≥ 1%	69.6% (53.8%, 85.7%)	84.1% (77.4%, 90.7%)	60.9% (50.4%, 73.6%)	88.6% (83.6%, 94.2%)	79.7% (67.4%, 90.4%)
sCr change ≥ 25%	21.7% (7.7%, 35.7%)	90.9% (86.0%, 97.3%)	46.0% (21.8%, 72.3%)	76.5% (73.2%, 79.9%)	57.0% (40.8%, 73.8%)

CONCLUSIONS:

- dd-cfDNA provides more accurate identification of active rejection than changes in serum creatinine (or single value) among DART patients with clinically indicated biopsy.
- Future studies will provide data on the performance of dd-cfDNA increase to predict rejection prior to or regardless of changes in serum creatinine.

REFERENCES:

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Disclosures

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MW is a consultant and investigator for CareDx
DH and JY are employees of CareDx.