# Donor-Derived Cell-Free DNA (dd-cfDNA) for Detection of Antibody-Mediated Rejection in Kidney Transplantation

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speaking on behalf of:

- James P. Yee, MD, PhD CareDx

and the lead DART study investigators:

- Daniel C. Brennan, MD, Washington University
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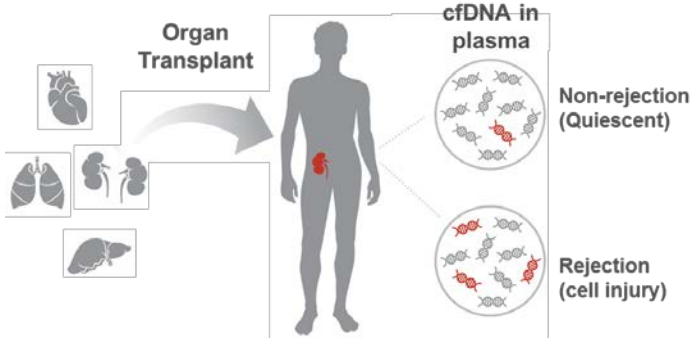
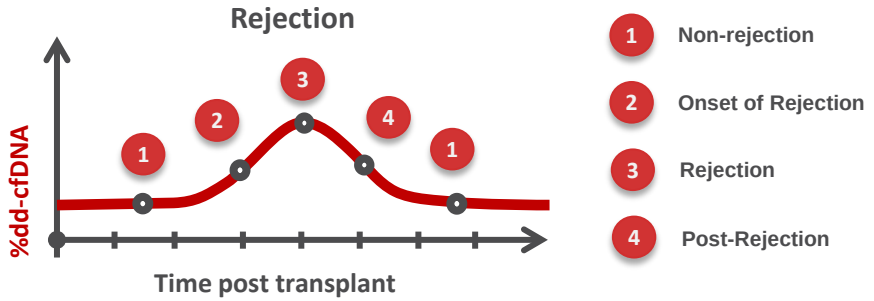
# Donor-Derived Cell-Free DNA (dd-cfDNA) is a Recently Validated Biomarker in Solid Organ Transplantation




Key Results from Peer-Reviewed Publications:

- dd-cfDNA is very low in stable transplant recipients [1]
  - De Vlaminck STM 2014 (heart), Grskovic JMD 2016 (heart), Bromberg JALM 2017 (kidney)
- dd-cfDNA is elevated at the time of rejection [2] [3]
  - De Vlaminck STM 2014, Grskovic JMD 2016, Bloom JASN 2017 (kidney)
- dd-cfDNA decreases following successful treatment [4]
  - De Vlaminck STM 2014, Grskovic JMD 2016
- Additional minor studies and major conference presentations in heart, kidney, liver, and lung suggest pan-organ applicability



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# AlloSure is the Only dd-cfDNA Test Analytically and Clinically Validated

| Description | Reference | Technology | Status |
|---|---|---|---|
| • dd-cfDNA diagnosis of acute rejection in Heart Tx | De Vlaminck, Sci Transl Med 2014 | Genotyping + shotgun SNP sequencing | Research-grade |
| • dd-cfDNA diagnosis of acute rejection in Lung Tx | De Vlaminck, PNAS 2015 | Genotyping + shotgun SNP sequencing | Research-grade |
| • ***Analytical Validation*** of AlloSure method for quantifying dd-cfDNA<br>• ***Clincal Validation*** of dd-cfDNA for diagnosis of acute rejection in **Heart** Tx | Grskovic, J Mol Diag, 2016 | Targeted SNP quantification | Clinical-grade |
| • ***Clinical Validation*** of dd-cfDNA for diagnosis of rejection in **Kidney** Tx | Bloom et al, J Am Soc Nephrol 2017 | Targeted SNP quantification | Clinical-grade |
| • Established dd-cfDNA **reference range** and biological variation in **Kidney** Tx | Bromberg et al, J Assoc Lab Med 2017 | Targeted SNP quantification | Clinical-grade |



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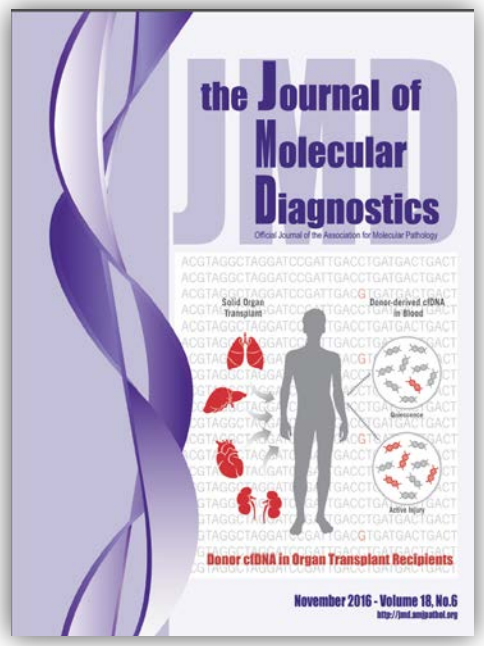
# Analytical Validity: AlloSure is a Sensitive, Accurate, and Precise Test for dd-cfDNA

| Metric | AlloSure Performance | Clinical Applicability |
|---|---|---|
| Lower limit of quantification | 0.20% | Results below 0.2% are not accurately quantified as different from zero |
| Quantifiable range | 0.20% -16% | • Results in kidney clinical validation studies range from 0% -8%<br>• Stable kidney recipient med. = 0.21%<br>• Critical decision point ~1% |
| Variability (CV) | 6.8% | Excellent test reproducibility |




*Grskovic et al., J Mol Diagn, 2016*

Clinical-Grade Test Development

- Analytical Validation studies completed with reference validated by an orthogonal technology according to CLSI recommended procedures
- Methods proficiency in accordance with standards for next-generation sequencing
- Bioinformatics pipelines validated and locked.



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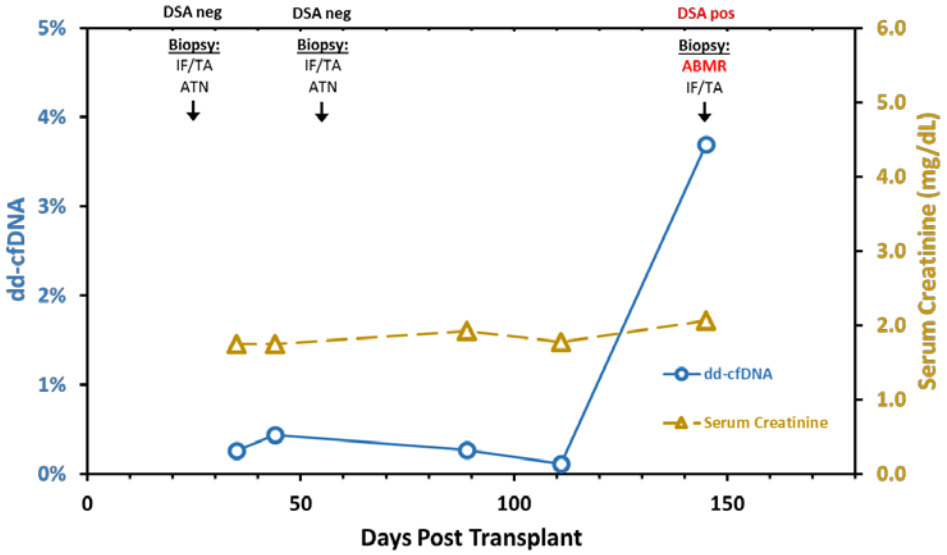
# Clinical Validity: AlloSure Accurately Discriminates Antibody-Mediated Rejection From No ABMR

| Performance Metric | AlloSure Test Performance at 1% Threshold |
|---|---|
| ROC/AUC | 0.87 (95% CI 0.75-0.97) |
| Sensitivity | 81% |
| Specificity | 83% |
| NPV | 96% |
| PPV | 44% |
| Median value | 0.21% (IQR 0.12%, 0.39%) |

DART Study: Landmark Biomarker Study in Kidney Transplantation with 14 Centers, 400 Patients

Patient with ABMR 5 months post transplant. AlloSure is elevated at the time of ABMR, but not at the time of negative biopsies at 1 and 2 months




*Bloom et al., J Am Soc Nephrol, 2017*
*Bromberg et al., J Assoc Lab Medicine, 2017*

# dd-cfDNA as a Biomarker in Kidney Transplant Trials

- dd-cfDNA provides a **quantifiable**, **direct** measure of allograft damage
- AlloSure has rigorous **analytical validity** and **clinical validity** with clear indication of clinical utility
- Applicability for integration into trials
  - Prognostic marker that forecasts the likely **course of disease**
  - Predictive marker that forecasts the likely **response to treatment**



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# dd-cfDNA as a Biomarker in Kidney Transplant Trials

**Potential Clinical Trial Applications of AlloSure:**

| Study Example | Existing Primary Endpoint | Potential Utilities of AlloSure |
|---|---|---|
| Evaluate efficacy and safety of treatment for acute ABMR | Proportion of subjects with new or worsening transplant glomerulopathy (TG) at 6 months after treatment initiation | • AlloSure can provide a quantifiable measurement of injury that can be established at baseline and repeated q2 to 3 weeks<br>• AlloSure can help ensure definition of baseline status<br>• Outcomes defined by AlloSure are more accurate and response to therapy trajectories can be more detailed than biopsy or serum creatinine can provide |

**AlloSure dd-cfDNA test is available for immediate use to support clinical trials to determine efficacy of new therapeutics for treating ABMR in kidney transplantation**



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# AlloSure is a Clinical-Grade Testing Service for Quantifying dd-cfDNA, a Clinically Validated Biomarker for Antibody-Mediated Rejection

- AlloSure dd-cfDNA testing is available from the CareDx Clinical Laboratory as a clinical diagnostic test
- Allosure testing is available for use to support drug development efforts underway for treatment of Antibody-Mediated Rejection



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