Performance of Next-Gen Sequencing Biomarker Tutivia™ in Setting of Kidney Delayed Graft Function

Abstract 7343

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Abstract

Purpose: The occurrence of delayed graft function (DGF) post-transplant presents clinically challenging complications. Patients will mostly require dialysis, have elevated creatinine and present clinical concerns for acute kidney injury (AKI); following acute reperfusion injury, evaluating risk of acute rejection (AR) secondary to the injury presents further challenge. Other risks may include pyelonephritis and polyoma viral nephropathy. Biomarkers are needed that can support medical management in challenging settings early post-transplant. Tutivia is a peripheral blood NGS RNA expression with algorithm test to produce a risk score correlated to acute rejection as defined by BANFF 2019 in kidney biopsy. This report analyses the clinical performance in setting of DGF.

Methods: In the clinical performance validation of Tutivia, 151 patients from 13 centers globally were enrolled prospectively in all-comers approach. Of these, 34 (22.52%) were reported to have experienced DGF; 4 were living donor (LD) recipients while 30 were deceased donor (DD) recipients. Of the 34 with DGF, 19 underwent for-cause biopsy while 15 went on to have surveillance biopsy at 3-6 months follow-up.

Results: In for-cause biopsy, 9 of 19 had AR findings, and of these, 8 had positive Tutivia results with the borderline case being the only negative Tutivia result. In the 10 patients with no AR, 5 had negative Tutivia and 5 positive. Upon examination of the 5 false positives, one had pyelonephritis, and one went on to be hospitalized with sepsis and expired on day 74. The third had multiple hospitalizations and went on to die of sepsis/respiratory distress at 7 months. The other two included findings of hematoma and hydronephrosis. In the 15 who later underwent surveillance biopsy at 3-6 months with Tutivia measured at or near that timepoint, 13 had no AR, and 2 had AR. Tutivia produced negative results in 12 of the 13 no AR as well as in a single each of borderline and IIB AR patient at time of surveillance.

Conclusion: While more data are needed to augment low numbers of patients in this analysis, in the setting of DGF following kidney transplant, Tutivia may be supportive in an indication setting producing positive results in all AR but one borderline. False positives may occur in context of sepsis or pyelonephritis. For those patients for whom the clinical course involved going on to be monitored by surveillance at 3-6 months, Tutivia sensitivity is low, but specificity is high and may be helpful in ruling out AR with NPV of 85.7%.

Background and Methods

Verici Dx has conducted a multicenter, international prospective all-comers kidney transplant clinical trial1 to validate the clinical performance of multiple biomarkers, including RNA Signatures comprised of a machine learning derived select set of gene expression features + algorithm. The output of the developed and validated RNA Signatures are risk assessment tests to inform clinicians in support of medical management decision making. Tutivia™ is a validated[2] prognostic, post-transplant peripheral blood test for the risk of all forms of acute rejection, borderline, TCMR 1A and higher, ABMR or mixed, as defined in histopathology of kidney biopsy according to BANFF2019.

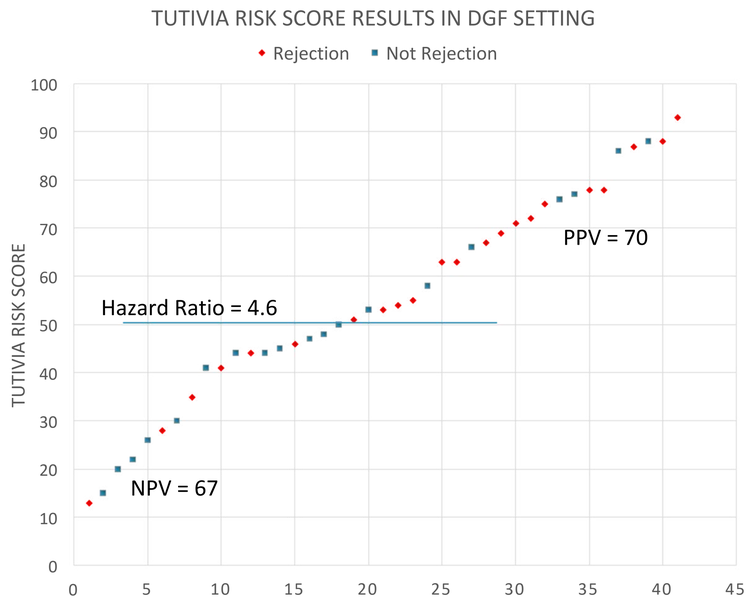
Acute kidney injury (AKI) may occur with transplantation; this may progress to delayed graft function (DGF), defined as the patient requiring dialysis at least once in the first week post-surgery. DGF is reported to occur in about 30% of deceased donor recipients but increases in prevalence when more marginal (DCD, high KDPI) organs are accepted. DGF is associated with higher risk of early acute rejection in the near term and shorter graft survival in the longer term. Evaluation of early clinical events can be complex, and immunosuppressive regimen toxicity and infection may also be suspected; in addition, serum creatinine is often high and not specific. No biomarker has currently been shown to provide sensitive and specific results in support of clinical evaluation in this setting. Herein we present the performance characteristics of Tutivia™ in patients who were identified to have delayed graft function (DGF) or who were evaluated in the setting of being worked-up for DGF following kidney transplant. Next, we evaluated later follow up biopsy and Tutivia™ results when available in this study group.

Clinical Samples: Patients were enrolled at the time of transplant surgery or during pre-transplant work-up for living donor (LD) recipients Table 1. Trial participants were followed post-transplant at 1, 3, 6, 12 and 24 month visits during which blood and urine were collected, and the study included a protocol biopsy at 3 and 12 months. Any clinically indicated visit, including for-cause biopsy, also included study specimen collection; all biopsies were read centrally, Table 2. Tutivia™ testing was performed in the Verici Dx CAP/CLIA accredited laboratory (Franklin, TN) according to published procedures.[2]

Table 1. Study Population

Study Population	Overall (N=41)		
Recipient age		**NO_TRANSPLANTS**	
Mean (SD)	54 (15.83)	0	35 (85.4%)
Median [Min, Max]	58 [22,75]	1	6 (14.6%)
Sex		**CIT**	
Male	27 (65.9%)	Mean (SD)	13.62 (6.85)
Female	14 (34.1%)	Median [Min, Max]	14 [0.65, 25]
Race		**HLA mm**	
Black	9 (22.0%)	0 - 4	13 (31.7%)
White	30 (73.2%)	5 - 8	25 (61.0%)
Missing	2 (4.9%)	Missing	3 (7.3%)
Ethnicity		**DE_NOVO_DSA**	
Hispanic/Latino	2 (4.9%)	No	39 (95.1%)
Not Hispanic/Latino	38 (92.7%)	Yes	2 (4.9%)
Missing	1 (2.4%)		
Donor Status		**Induction Medication**	
LRD	2 (4.9%)	ATG/Thymo	24 (59%)
LURD	5 (12.2%)	IL2RA	11 (27%)
SCD	17 (41.5%)	Campath	6 (14%)
ECD	10 (24.4%)	Methylprednisolone	41 (100%)
DCD	7 (17.1%)		

Figure 1. Tutivia Results Event Chart



Results

Table 2. Biopsy

HP Findings	Number (%)
ABMR	4 (10%)
Mixed	8 (20%)
TCMR IA+	6 (15%)
Borderline	4 (10%)
Death	3 (7%)
Graft Loss	9 (22%)
No Rejection/normal	19 (46%)
AKI/ATN	7 (17%)
BK/CMV	0 (0%)
Bacterial infect	2 (5%)
TMA	4 (10%)
Other	3 (7%)

A cohort of 41 patients participating in the Verici Dx clinical trial, Table 1, were identified through reporting to have presented with concern for AKI, DGF or AR workup following kidney transplant surgery. The primary indication was rising creatinine. All patients in this evaluation had a biopsy performed, Table 2, and a blood drawn that was analyzed using Tutivia™ test, Figure 1. Performance assessment for Tutivia™ accuracy of prognostic risk classification was done by comparison to the current gold standard of histopathologic findings by kidney biopsy according to current BANFF criteria. There were 7 false positives which included 4 ATI/ATN and 2 pyelonephritis diagnoses. When examining the false negative results, 3 of 6 (50%) were results >40, falling just below the clinical cut-point.

Tutivia ™ demonstrated both a favorable PPV, 70%, and NPV, 67%, highlighting this test's balanced accuracy particularly in a complex patient population with high event rate of 22/41 (54%). Moreover, the hazard ratio indicates that patients with high-risk classification results are nearly 5 times more likely to experience AR than those with low classification results.

Conclusions and Discussion

- Current biomarkers of injury, including serum creatinine, have been shown to be poorly predictive of acute rejection (AR) and to lack sensitivity.
- Yet, rising creatinine levels are often the clinical indicator for further evaluation. Early post-transplant, elevated creatinine levels may raise concern for infection, immunosuppressive drug toxicity, AKI, ATN, DGF and AR without clarity into clinico-pathologic processes. Not all patients with AKI develop ATN, DGF or AR.
- Biomarkers are needed to identify high and low risks of AR in this complex clinical milieu of AKI and DGF with or without AR. To date, new developments in biomarker technologies lack clear evidence of clinical performance in this setting.
- The favorable hazard ratio, PPV and NPV in Tutivia™ clinical performance in this particularly challenging population demonstrates that RNA Signature Tutivia™ informs prognostic interpretations supporting clinical management.
- Limitations include a limited size study cohort, n = 41, and occurrence of false positives in setting of pyelonephritis.
- This level of evidence in correlating a blood-based transcriptomic signature + algorithm with a rejection phenotype based on histopathology in the kidney biopsy represents an advancement to support clinician that has not been previously offered in biomarker transplant biology.
- More studies are needed to evaluate the performance of Tutivia™ longitudinally and to evaluate correlation with long-term outcomes.

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