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Serial Peripheral Blood Gene Expression Profiling to Assess Immune Quiescence in Kidney Transplant Recipients with Stable Renal Function

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 V. Ram Peddi
BCDE 1 Parul S. Patel
ABCDEF 2 Courtney Schieve
ABCDEF 2 Stan Rose
ABCDEF 2 M. Roy First

1 Department of Transplantation, California Pacific Medical Center, San Francisco, CA, U.S.A.
2 Transplant Genomics Inc., Mansfield, MA, U.S.A.

Corresponding Author: V. Ram Peddi, e-mail: peddir@sutterhealth.org
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Background: TruGraf is a blood-based biomarker test that measures differential expression of a collection of genes that have been shown to correlate with surveillance biopsy results. However, in the majority of U.S. transplant centers, surveillance biopsies are not performed. The objectives of this study were to evaluate the clinical validity of TruGraf in stable kidney transplant recipients and to demonstrate the potential clinical utility of serial TruGraf testing in a center not utilizing surveillance biopsies.

Material/Methods: Serum creatinine levels, TruGraf testing at multiple time points, and subsequent clinical follow-up were obtained for 28 patients.

Results: Overall concordance of TruGraf results, when compared with independent clinical assessment of testing, was 77% (54/70) for all tests; 79% (22/28) for test 1, 75% (21/28) for test 2, and 79% (11/14) for test 3. The negative predictive value (NPV) was 98.0%. Analysis of clinical utility indicated that 77% of TruGraf results would have been useful in patient management.

Conclusions: Our results indicate the value of serial TruGraf testing in those transplant centers that do not perform surveillance biopsies as part of their standard of care. The high negative predictive value indicates the ability of TruGraf to confirm immune quiescence with a high degree of probability in patients with a Transplant eXcellence (TX) result, without the need to perform a surveillance biopsy.

MeSH Keywords: **Biological Markers • Biopsy • Graft Rejection • Kidney Transplantation**

Abbreviations: **CLIA** – Clinical Laboratory Improvement Amendments; **LDT** – Laboratory Developed Test; **not-TX** – not Transplant eXcellence; **NPV** – negative predictive value; **PI** – principle investigator; **PPV** – positive predictive value; **subAR** – subclinical acute rejection; **TGI** – Transplant Genomics Incorporated; **TX** – Transplant eXcellence

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Background

A key contributor to long-term kidney graft loss is subclinical immune injury that manifests as undetected subclinical acute rejection (subAR), perhaps due to under-immunosuppression, leading to chronic rejection [1–3]. Surveillance biopsy is currently the only means to rule out or detect subAR, which is defined as a transplant recipient with stable renal function and a kidney biopsy with histologic features of acute rejection (borderline or higher). A recent survey of transplant centers indicated that 62% do not perform surveillance biopsies and 21% perform surveillance biopsies only in high-risk patients; the reasons cited for not performing surveillance biopsies include low yield, will not change patient outcome, inadequate staffing, insurance barriers, and too many transplants [4]. In addition, the currently accepted criterion standard for diagnosing rejection is a biopsy of the transplanted kidney. However, the internationally accepted Banff Classification of rejection has 2 main weaknesses, namely, poor reproducibility, and lack of independent validation [5]. The issue of borderline changes and the lack of mechanistic understanding are particularly noteworthy, as this category of rejection is present in 80% of biopsies with subAR [6]. Based on surveillance biopsies, the rate of subAR in subjects with stable renal function is approximately 25% in the first year after transplant [6]. Most importantly, untreated subAR, including cases of borderline rejection, has been shown to be associated with worse long-term outcomes in some studies [6–9]. Programs that do not perform surveillance biopsies are thus missing 100% of these patients, who typically are only recognized when their subclinical immune injury has progressed to the point that renal dysfunction becomes clinically evident. In the absence of this information, there is an urgent need for a non-invasive test that can help stratify patients into those that are highly likely to be immune quiescent *vs.* those who are not.

Furthermore, a major problem with surveillance biopsies is that they cannot be performed frequently; typically, 1–2 times per year in the first 3 years [4,6]. However, a patient might develop subclinical immune injury at any time point during the first 3 years and beyond. A center that does not perform surveillance biopsies misses 100% of such patients, and has no way of confirming that the vast majority of stable patients are truly immune quiescent.

The TruGraf blood test (Transplant Genomics, Inc., Mansfield, MA, USA) is a Laboratory Developed Test (LDT) available exclusively through the Clinical Laboratory Improvement Amendments (CLIA) certified laboratory at Transplant Genomics, Inc. [10]. TruGraf enables proactive serial testing in kidney transplant recipients with stable renal function [10–14] by measuring differentially expressed genes in peripheral blood to determine whether there is high likelihood that silent rejection can be ruled out in a patient, indicating that they are likely to be immune quiescent and thus adequately immunosuppressed [10–14]. TruGraf relies on analysis of gene expression signatures that profile the expression levels of many genes associated with a given phenotype, thereby differentiating a state of Transplant eXcellence (TX, indicating adequately immunosuppressed) from not-TX. Details of the gene expression profile have been published previously [12].

As previously described [10], the development of the TruGraf test was based on the discovery and validation of "signatures" (patterns of gene expression) derived from the peripheral blood in 2 populations of patients: (i) patients following kidney transplantation with stable renal function and surveillance biopsies that revealed no evidence of histologic rejection (designated as TX), and (ii) patients following kidney transplantation not meeting the strict criteria for TX (designated as not-TX) [10].

A TruGraf blood test result of "TX" in a kidney transplant recipient with stable renal function would enable physicians to identify, with a high degree of confidence, patients in whom no intervention is necessary, allowing for routine follow-up, including serial TruGraf testing, without the need for an invasive surveillance biopsy [12–14]. This is of significance because surveillance biopsies can be logistically challenging for patients and transplant centers, cause discomfort for patients, are expensive for the healthcare system, carry risk of complications including graft loss, and yield only a ~25% rate of positivity [4], indicating that ~75% of surveillance biopsies are unnecessary and could be avoided [6].

TruGraf is the initial non-invasive test to be evaluated for clinical applicability in ruling out subAR in patients with stable renal function (i.e., the probability that a patient is in a state of immune quiescence and adequately immunosuppressed *vs.* rejecting and in need of additional evaluation and/or the consideration of a change in therapy), thereby enabling confirmation of immune quiescence in the vast majority of patients, and early detection of immune activation in others, with the potential to reverse the process prior to the development of irreversible damage [6].

Several studies describing the development, clinical validity, and performance metrics of TruGraf have been published, all based on comparisons of TruGraf results to histological analysis of tissue obtained by surveillance biopsy at the same time as blood was collected [6,10–14]. In the present study, serial TruGraf testing was performed in kidney transplant recipients with stable renal function to evaluate and demonstrate the clinical utility of serial testing in a center that does not perform surveillance biopsies.

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Material and Methods

Study population and clinical parameters

A prospective, non-interventional clinical study was performed involving kidney transplant recipients not monitored by surveillance biopsy. The California Pacific Medical Center Institutional Review Board (IRB) concluded that this study was IRB-exempt because the test was not used for patient management and no patient clinical data were provided to the Transplant Genomics, Inc. clinical laboratory other than information normally provided on a laboratory test requisition form. A total of 28 subjects were tested with either 2 serial tests performed (Cohort A; n=14) or 3 serial tests performed (Cohort B; n=14). In no instances were results of the TruGraf test used to guide patient management, which was decided upon by the clinicians at the center. Inclusion criteria were patients >90 days after transplantation with stable renal function, defined as a serum creatinine level ≤2.3 mg/dL and an increase in creatinine of <20% compared to the average of a minimum of 2–3 preceding values. Exclusion criteria were subjects with unstable renal function, using the criteria described above. No patients were excluded based on age, sex, ethnicity, HLA-type, immunosuppression, or donor type and induction therapy, since the purpose of the study was to include recipients receiving the participating center's standard of care. Sample collection was performed during a routine lab blood draw, with samples simultaneously collected for renal function evaluation and TruGraf testing.

Patient follow-up was carried out for 1 year after performing the first TruGraf test.

TruGraf testing and concordance analysis

The TruGraf® Blood Gene Expression Test is a microarray-based assay that analyzes gene expression profiles in the peripheral blood. This gene expression profile is associated with either a normal protocol kidney biopsy (Transplant eXcellence – TX) or the absence of a normal biopsy (not-TX) in patients with stable renal function [10,12]. All aspects of discovery and external validation of the TruGraf test were performed on blood samples paired with biopsies from prevalent cohorts. For the purpose of validation, the model derived from pre-selected bio-informatics and the threshold used to test performance on the discovery cohort were locked. These data led us to use this approach for external validation in clinical studies [13,14].

For each TruGraf test, we drew two 2.5-ml PAXgene RNA tubes of blood and sent them to the TGI CLIA lab for analysis, and results were provided to the principal investigator (PI) in real time. The molecular testing laboratory was blinded to the clinical assessment and renal function, and samples were assigned a de-identified number only. The TruGraf blood test results were reported dichotomously as TX or not-TX, with not-TX representing the positive result. The clinical phenotypes were determined independently by the PI at the center based on their assessment of the renal function, along with other laboratory and clinical data. Based on comparing the clinical phenotypes and the TruGraf molecular phenotypes, the PI then made an assessment as to whether the TruGraf results were concordant or not with the clinical phenotype. Based on this concordance analysis, each TruGraf test result was classified as:

- True negative – TruGraf test result TX; physician assessment clinically stable.
- True positive – TruGraf test result not-TX; physician assessment clinically unstable.
- False negative – TruGraf test result TX; physician assessment clinically unstable.
- False positive – TruGraf test result not-TX; physician assessment clinically stable.

Based on these assessments, the TruGraf blood test result and the clinical phenotype were then analyzed for accuracy (concordance), the negative predictive value (NPV)

and positive predictive value (PPV) of the test, as well as the sensitivity and specificity of the test.

Clinical utility

Clinical utility was evaluated retrospectively to determine the potential impact of TruGraf results on patient treatment decisions. For each result, the PI was asked if the result would have influenced patient management regarding immunosuppression dosing, altering the frequency of clinic visits, or deciding on whether or not a biopsy was indicated.

Results

Patient demographics were as follow. The mean age was 59 years (range 30–78 years). The transplant was the first transplant in 25 patients, the second transplant in 2 patients, and the third transplant in 1 patient. The kidney source was a deceased donor in 27 cases and a living donor in 1 case. Recipient race was white in 12 cases, Hispanic in 8 cases, African American in 4 cases, and Asian in 4 cases.

TruGraf testing was performed in 2 cohorts, with Cohort A receiving 2 sequential tests and Cohort B receiving 3 sequential tests. Clinical characteristics of the study cohorts are summarized in Table 1.

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Table 1. Clinical characteristics of testing cohorts.

Characteristic	Cohort A	Cohort B
Total Subjects	14	14
Male	6	5
Female	8	9
Average age at time of enrollment, (median)	56 (63)	63 (65)
Serum creatinine level (mg/dL) at time of TruGraf testing (mean±SD)		
1st test	1.09±0.208	1.01±0.367
2nd test	1.03±0.233	0.95±0.338
3rd test	NA	0.89±0.309
Testing Interval		
Time between Test 1 and Test 2 (days)	156	93
Time between Test 2 and Test 3 (days)	NA	200

NA – not applicable

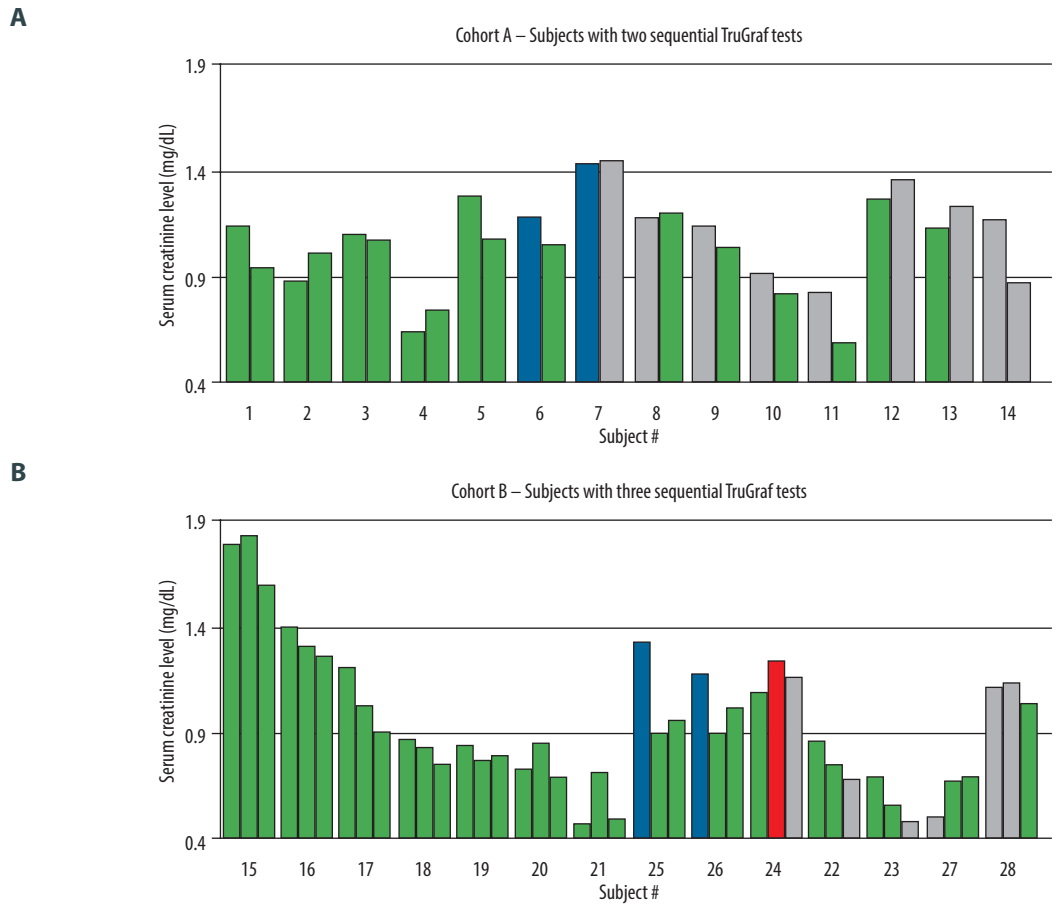

Figure 1. Serum Creatinine levels (mg/dL) and TruGraf results in patients with 2 sequential tests Cohort A (**A**) and 3 sequential tests Cohort B (**B**). Green – True Negative; Blue – True Positive; Red – False Negative; Grey – False Positive.

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Table 2. Sequential results of the TruGraf blood test and comparison with clinical phenotype in 28 kidney transplant recipients with stable renal function.

	Clinical phenotype TX	Clinical phenotype not-TX
TruGraf Blood Test TX	50	1
TruGraf Blood Test not-TX	15	4

Accuracy=54/70 (77%); Accuracy of TruGraf TX result=50/51 (98%); NPV=98.0; PPV=21.1; Sensitivity=80.0; Specificity=76.9.

A total of 70 TruGraf tests were conducted, with 14 patients in Cohort A receiving a total of 28 tests and 14 patients in Cohort B receiving a total of 42 tests.

The sequential TruGraf test results and serum creatinine levels for Cohort A subjects having 2 tests are shown in Figure 1A, and results for the Cohort B subjects having 3 tests are shown in Figure 1B.

The overall accuracy of the TruGraf test, in which the TruGraf test result was concordant with the physician's clinical assessment of the patient, was 77% (54/70), and the NPV of the test was 98.0% (Table 2).

In addition, overall performance of TruGraf did not change over the time points measured; concordance was 78.6% (22/28) with Test 1, 75.0% (21/28) with Test 2, and 78.6% (11/14) with Test 3, indicating that the accuracy of the TruGraf test remains stable over multiple time points. There was only 1 (1.4%, 1/70) false negative test result (a patient incorrectly called TX). A false positive result occurred in 15/70 (21.4%) of TruGraf tests. Importantly, we note that these observed TruGraf performance metrics are essentially the same as those reported for TruGraf when the standard for comparison was histological analysis of tissue from a surveillance biopsy obtained at the same time as when blood was collected [12–14].

Analysis of Cohort A (14 subjects having 2 tests) reveals that the initial test result was true negative in 7 subjects, true positive in 2 subjects, and false positive in 5 subjects. While the concordance between the TruGraf test result and the clinical assessment was similar at test 1 (78.6%) and test 2 (75.0%), test results changed in individual patients. Of the 7 true negative results for test 1, 5 remained true negative at test 2, and 2 changed to a false positive result. Of the 5 false positive results for test 1, 4 changed to a true negative result and 1 remained a false positive at test 2.

Evaluation of Cohort B (14 subjects having 3 tests) revealed that in 7 subjects, the result was a true negative at all 3 testing time points. Two subjects with an initial result of true positive were true negative on both subsequent tests. In both of these patients there was a decrease in the serum creatinine level, and both were judged to be clinically stable by the PI. Two subjects had an initial test result of false positive and changed to a true negative result by the third test. Two subjects had 2 true negative results that changed to a false positive at the third test.

The PI Indicated that serial TruGraf testing would have had an impact on patient management. TruGraf results would have supported the PI's decision on how to manage a patient with stable serum creatinine in 77% of cases.

All subjects were followed for 1 year after the first TruGraf blood test. One patient died with a functioning graft, and the final TruGraf test result was not-TX in this subject. The remaining 27 subjects were alive with functioning grafts at 1-year follow-up. The median eGFR in these subjects was 64 mL/min (mean 70.7 mL/min, range 34–118 mL/min). A single patient had an acute rejection episode during the follow-up period; in this subject the last TruGraf test was also not-TX.

Discussion

Silent subclinical rejection is frequent and is a significant contributor to worse long-term outcomes for kidney transplant recipients [1,3]. Until now, subAR could only be ruled in or out by invasive and risky per protocol surveillance biopsies, resulting in a significant number of unnecessary biopsies creating unnecessary risk to patients. Thus, non-invasive tests are clearly needed to identify patients with stable renal function who are harboring subAR in their grafts. A "rule out" test results in the reduction of a large proportion of protocol biopsies in programs that currently utilize these; in those that do not, subjecting far fewer patients to the risks of biopsies together with a reduction in the number of unnecessary (negative) biopsies provides an attractive monitoring strategy. TruGraf is the only non-invasive test designed and validated for use in ruling out silent subAR in kidney transplant recipients with stable renal function that has been approved by Medicare as an alternative to surveillance biopsies. Additionally, the test may be used in situations when it is not feasible to do a biopsy, such as in a patient on anti-coagulation therapy, and in subjects at high risk for developing acute rejection such as in the use of extended-criteria donors with delayed graft function, those with pre-existing DSA, and those who develop *de novo* DSA after transplantation. Non-invasive blood testing can be done more frequently than surveillance kidney biopsies, is significantly less invasive, less painful and risky for patients,

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and can result in considerable cost savings to the health delivery system.

Our study demonstrates the clinical validity and potential clinical utility of serial peripheral blood gene expression profiling in kidney transplant recipients with stable renal function. Here, we report the clinical performance of the TruGraf test at a transplant center that does not perform surveillance biopsies. The frequency of serial TruGraf testing was selected based on a previous study [6]; however, we believe TruGraf could be performed to confirm immune quiescence at any time without the need to perform a surveillance biopsy.

In this study, outcomes were measured by assessing renal function (stability or change in serum creatinine levels) when using TruGraf serially. The overall performance of TruGraf is consistent over multiple time points, and its accuracy was similar at all time points. The overall accuracy (77%) and accuracy of a TruGraf TX result (98%) is similar to that described in other studies [12–14]. Furthermore, our overall accuracy is in line with the findings that ~75% of surveillance biopsies show normal histology [6].

At initial testing, there were 6 subjects with a false positive result. Five (83%) of these converted to a true negative result; all had stable renal function, again emphasizing the value of serial TruGraf testing. A not-TX result in a subject who is clinically stable (a false positive result) does not indicate a need for a change in patient management; rather, it indicates the need to follow the patient more closely and for more frequent TruGraf testing.

There were 4 subjects with an initial true positive result. Three (75%) of these converted to a true negative result on subsequent testing, and all 3 experienced a fall in serum creatinine level. This represents a group of patients who might have been treated if such a decision had to be based on a single positive test result, yet shows resolution when tested serially. These results indicate that serial TruGraf testing offers even greater potential than once-a-year testing as a practical surrogate to surveillance biopsies, since it allows for trends to be visualized over time, an advantageous feature during immunosuppression minimization, treatment response evaluation, and other instances when frequent and serial monitoring is desired.

In light of the high NPV we observed (98%), one can have great confidence in a negative result of TX. Only 1 patient (1.4%) changed from a true negative to a false negative. This subject had a minor increase in the serum creatinine level. This would have no impact on outcome in sites not doing surveillance biopsies, as the assumption in these sites is that all stable patients are TX; therefore, there is no added risk of a false TX (false negative) diagnosis.

Over 60% of transplant programs in the United States do not perform surveillance biopsies [4]. The assumption is that all of the patients with stable renal function are indeed stable, yet we know that ~25% have subAR [6]. The TruGraf test provides information about which of those patients are really stable or are in a state of immune quiescence, with a high degree of confidence. The remaining subjects may be harboring subAR and need to be monitored more closely, including with more frequent TruGraf testing.

Limitations of the present study are the relatively small sample size, the short period of follow-up, and the fact that TruGraf is a new test and the PI involved in this study did not have any prior experience with the test at the beginning of the study [13,14]. Therefore, the PI was not prepared to make patient management decisions based on TruGraf results, which might underestimate the changes in patient management once the test is fully integrated into the diagnostic workup of kidney transplant recipients.

Clinical utility of a new diagnostic test is generally accepted as meaning that a test affects or supports a physician's treatment decision, and that physicians consider the use of the test as reasonable and necessary in order to provide optimal care for their patients [15–17]. In the present study, the principal investigators expressed satisfaction with the ability to confidently confirm stability in 77% of patients, and led them to independently conclude that TruGraf testing is reasonable and is a promising alternative to surveillance biopsy. With sufficient experience, the PI may be able to eventually use TruGraf results in future studies to provide optimal care for stable patients undergoing a reduction of immunosuppression.

Non-invasive blood testing can be done more frequently than surveillance kidney biopsies, is significantly less invasive, less painful and risky for patients, and can result in a considerable cost savings to the health delivery system.

We find our conclusions regarding clinical utility to be important because they establish the potential for TruGraf testing to provide clinically useful and necessary data at a transplant center not performing surveillance biopsies, where physicians lack histological data to confirm immune quiescence in their stable patient population.

Conclusions

Our results of clinical performance and clinical utility show that serial TruGraf testing could be routinely performed at a center not utilizing surveillance biopsies. The overall performance of TruGraf was consistent over multiple time points, and results of TX confirm immune quiescence in kidney transplant

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recipients with stable renal function. Based on our results, we suggest that implementation of serial TruGraf testing could be very helpful as an additional clinical tool for use in making treatment decisions in kidney transplant recipients with stable renal function when surveillance biopsy is not collected.

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Conflict of interests

Courtney Schieve, Stan Rose and M. Roy First are full-time employees at Transplant Genomics, Inc., who developed the TruGraf test.

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