Anthem FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE

Medical Policy

Subject:	TruGraf Blood Gene Expression Test for Transplant Monitoring		
Document#:	GENE.00058	**Publish Date:**	10/06/2021
Status:	New	**Last Review Date:**	08/12/2021

Description/Scope

The TruGraf® blood gene expression test is a blood-based gene expression assay designed to identify transplant recipients who are inadequately immunosuppressed.

Note: Please see the following related document(s) for additional information:

- **CG-TRANS-02 Kidney Transplantation**
- **LAB.00038 Cell-free DNA Testing to Aid in the Monitoring of Kidney Transplants for Rejection**
- **TRANS.00008 Liver Transplantation**

Position Statement

Investigational and Not Medically Necessary:

TruGraf blood gene expression test is considered investigational and not medically necessary for monitoring immunosuppression in transplant recipients and for all other indications.

Rationale

Following a transplant, monitoring the health of the allograft is crucial for detecting evidence of rejection as early as possible. Early detection of rejection enables individualized adjustments to immunosuppressive therapy, thereby decreasing the likelihood of transplant failure. The most widely accepted method for surveillance of renal and liver rejection is achieved by monitoring blood and urine laboratory values, such as serum creatinine levels and liver function tests. Confirmatory diagnosis is made by histologic analysis of the allograft via needle biopsy, the current gold standard for diagnosis. While serum creatinine, liver function tests, and other blood and urine laboratory values provide valuable insight, they are not specific or sensitive for transplant rejection. Use of a more accurate biopsy for frequent, routine monitoring is not ideal due to the invasiveness and risks of the procedure. Use of TruGraf gene expression test for measurement of genes differentially expressed during acute transplant rejection has been proposed as a noninvasive testing method

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

that may be more specific than routine laboratory monitoring while enabling more frequent monitoring of kidney and liver allografts than biopsy permits.

TruGraf Kidney

In 2019, Marsh and colleagues conducted a retrospective data analysis of peripheral blood samples from 192 stable kidney allograft recipients at 7 transplant centers to evaluate the efficacy of the TruGraf classifier. The molecular testing laboratory evaluating TruGraf results was blinded to the concordant renal function and biopsy test results that were comparatively analyzed to determine the resulting dichotomous TruGraf score ("stable"/immune quiescence vs "not stable"/renal dysfunction and/or rejection). Overall, TruGraf accuracy (concordance between TruGraf results and clinical and/or biopsy results) was 74% (142/192), and a result of 'stable' graft function was accurate in 116 of 125 samples. The negative predictive value for TruGraf was 90%, with a sensitivity and specificity of 74% and 73%, respectively. Results did not significantly differ in transplant recipients with a biopsy-confirmed diagnosis vs. those without a biopsy. Prospective, long-term study is warranted to establish and fully characterize the clinical utility of TruGraf in kidney transplant recipients.

In 2019, First and colleagues conducted an additional retrospective analysis of the 192 kidney transplant recipients described above to compare TruGraf test results with physician assessment and resulting management decisions. In 168 of 192 (87.5%) cases, the 45 physicians surveyed indicated the TruGraf results impacted their decisions in management of transplant recipients. The study indicated that TruGraf results supported physicians' decisions on transplant management 87% (39/45) of the time, and 93% of physicians queried reported they would use serial TruGraf testing in future kidney transplant management. A total of 21 of 39 (54%) clinicians indicated that TruGraf confirmed their decision that no intervention was needed, and 17 of 39 (44%) indicated more specifically that TruGraf results helped confirm their decision to not perform a surveillance biopsy. Prospective evaluation of the TruGraf's impact on clinically relevant outcomes, such as graft survival and overall survival relative to current methods of surveillance (e.g., peripheral blood values and biopsy) are indicated.

In 2019, Friedewald and colleagues conducted a multicenter study to continue investigating development of TruGraf's validity using paired blood and biopsy samples. Two observational cohorts were recruited and enrolled: (1) multi-center cohort receiving standard of care with peripheral blood sample monitoring (every 2 weeks) for biomarker determination (n=253) and (2) a single-site cohort receiving standard of care without peripheral blood monitoring (n=129). Study inclusion criteria included adults (18 years or older) undergoing

a planned kidney transplant. Standard of care follow-up biopsies for both cohorts consisted of sampling at 2 to 6, 12, and 24 months post-transplant in addition to for-cause biopsies for acute renal dysfunction. At a prespecified threshold, 72% to 75% of kidney transplant recipients achieved a 'negative' result which correlated with the absence of subacute rejection (negative predictive value ([NPV], 78%-88%), while a positive result was achieved in 25% to 28% of samples which correlated with the presence of subacute rejection (positive predictive value [PPV], 47%-61%). Less than 50% of samples achieved histologic improvement of subacute rejection on repeat biopsy following treatment; the TruGraf algorithm reliably predicted nonresponders. Continued investigation is warranted demonstrating TruGraf's ability to improve clinical outcomes equivalent to or beyond standard of care surveillance in the post kidney transplant setting.

In 2020, Peddi and colleagues conducted a prospective, non-interventional study enrolling kidney transplant recipients not monitored by surveillance biopsy to evaluate the clinical validity and potential utility of TruGraf in stable kidney transplant recipients. A total of 28 transplant recipients (> 90 days post-transplant with stable graft function) were enrolled and monitored for transplant health through serial testing of serum creatinine levels and TruGraf gene expression profiling (2 to 3 tests performed). Overall concordance of TruGraf results compared to independent physician assessment was 77% (54/70) for all tests (TruGraf tests 1, 2 and 3). The NPV was 98.0%. Retrospective post-hoc analysis indicated that 77% of TruGraf results would have been useful in physician management decisions. Authors conclude that, in centers where surveillance biopsy is not performed, TruGraf may have utility. Further study demonstrating the net health benefit from TruGraf, relative to standard of care (e.g., serum creatinine) is warranted.

In 2021, Ang and colleagues conducted a single-center, prospective study of 90 consecutive kidney transplant recipients with with standard biopsy results collected 6 months post-transplant. TruGraf testing was concurrently performed at the time of biopsy. TruGraf resulted in a negative test in 67 subjects, 54 of which had a normal biopsy. A total of eight transplant recipients had a true positive result. Based on the results of this cohort study using TruGraf, a biopsy was performed in 15 subjects with a false-positive test, and sub-acute rejection was missed in 13 subjects with a false-negative test, resulting in a PPV of 35% and a NPV of 81%. Authors conclude that overall, standard biopsy could have been avoided in 54 (60%) of kidney transplant recipients in the study. Investigation of TruGraf's performance, including long-term clinically meaningful outcomes, in the setting of a randomized clinical trial is warranted.

Several observational cohort studies are underway to continue to establish and characterize the TruGraf's clinical utility, including a 24-month, 2000 participant study with clinically relevant outcomes, including biopsy proven acute rejection, graft loss, or a decrease from baseline in eGFR > 10 mL/min (NCT04491552).

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

TruGraf Liver

In 2020, Levitsky and colleagues conducted a discovery and validation study of TruGraf liver by performing a retrospective cohort analysis of 75 liver transplant recipients' gene expression profiles. Blood gene profile samples were collected through serial blood sampling up to 12 months post-transplant and paired with biopsies showing acute rejection, acute dysfunction without rejection, or samples with stable graft. Gene expression profiles were analyzed using random forest models to generate a 36-gene classifier training set designed to distinguish acute rejection from stable allografts. Analysis of the resulting classifier yielded an accuracy of 0.77, sensitivity 0.57, specificity 0.82, positive predictive value 0.47, and negative predictive value of 0.87 for acute rejection compared to stable graft. Authors conclude that use of a diagnostic blood-based gene expression test is feasible prior to acute rejection-associated graft injury and that "further studies are needed to evaluate its utility in precision-guided immunosuppression optimization following liver transplant." Currently, there are no registered clinical trials of TruGraf liver.

Background/Overview

As of December 2019, the Organ Procurement and Transplantation Network (OPTN) reported that there were about 95,000 Americans on the wait-list for kidney transplantation with approximately 21,000 kidney transplants performed in that same year. Subacute rejection affects 35% of kidney transplant recipients in the first 2 years post-transplant The total number of living kidney transplant recipients with a functioning graft is projected to surpass 250,000 in the next few years. Approximately 8,000 liver transplants occur in the US per year with an average of just 50-75% of grafts surviving the first-year post-transplant (OPTN, 2019).

A solid organ transplant (e.g., liver or kidney) involves the surgical removal of a diseased organ and replacement with a healthy organ from a deceased or living donor. Monitoring the health of the transplant is vital to the survival of both the transplant and the transplant recipient. The most widely accepted method for the surveillance of an allograft for rejection is monitoring of serum laboratory values with confirmatory diagnosis achieved by histologic analysis of the allograft via needle biopsy, the current gold standard. Immunosuppressive drug therapy is adjusted according to transplant monitoring with the end-goal of preserving the allograft's function, hence delaying or preventing graft rejection (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2018).

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

TruGraf Blood Gene Expression Test is designed to be a non-invasive blood test with the ability to inform clinicians if transplant recipients are adequately immunosuppressed or not, sooner than other available methods (i.e., serum creatinine increases, liver function tests, or donor-derived cell-free DNA). TruGraf uses RNA microarray technology to determine whether a blood gene expression profile is more similar to that obtained from a 'transplant excellence' reference population classified by biopsy (i.e., adequately immunosuppressed) or not (subacute rejection; inadequately immunosuppressed). To date, subclinical acute rejection has only been diagnosed by biopsy.

Definitions

Allograft: The transplant of an organ or tissue from one individual to another of the same species with a different genotype; for example, a transplant from one person to another, but not an identical twin.

Chronic renal disease: The permanent loss of kidney function.

End stage renal disease: Persistent decline in renal function as documented by falling creatinine clearance in an individual diagnosed with a renal disease whose natural history is progression to renal impairment requiring renal replacement (dialysis or transplant).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81479	Unlisted molecular pathology procedure [when specified as TruGraf Blood Gene Expression Tests]

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. **Ang A, Schieve C, Rose S, et al. Avoiding surveillance biopsy: Use of a noninvasive biomarker assay in a real-life scenario. Clin Transplant. 2021; 35(1):**
2. **First MR, Peddi VR, Mannon R, et al. Investigator assessment of the utility of the TruGraf molecular diagnostic test in clinical practice. Transplant Proc. 2019; 51(3):729-733.**
3. **Friedewald JJ, Kurian SM, Heilman R, et al. Development and clinical validity of a novel blood-based molecular biomarker for subclinical acute rejection following kidney transplant. Am J Transplant. 2019; 19(1):98-109.**
4. **Levitsky J, Asrani SK, Schiano T, et al; Clinical Trials in Organ Transplantation - 14 Consortium. Discovery and validation of a novel blood-based molecular biomarker of rejection following liver transplantation. Am J Transplant. 2020; 20(8):2173-2183.**
5. **Marsh CL, Kurian SM, Rice JC, et al. Application of TruGraf v1: A novel molecular biomarker for managing kidney transplant recipients with stable renal function. Transplant Proc. 2019; 51(3):722-728.**
6. **Peddi VR, Patel PS, Schieve C, et al. Serial peripheral blood gene expression profiling to assess immune quiescence in kidney transplant recipients with stable renal function. Ann Transplant. 2020; 25:e920839.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Centers for Disease Control and Prevention. Chronic Liver Disease and Cirrhosis. Available at: https://www.cdc.gov/nchs/fastats/liver-disease.htm. Accessed on June 16, 2021.**
2. **Centers for Disease Control and Prevention. National chronic kidney disease fact sheet. Available at: https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf. Accessed on June 08, 2021.**
3. **National Institute of Diabetes and Digestive and Kidney Diseases. Kidney Transplant (NIDDK). Kidney Transplant. Updated January 2018. Available at: https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/kidney-transplant. Accessed on June 08, 2021.**
4. **National Institute of Diabetes and Digestive and Kidney Diseases. Kidney Transplant (NIDDK). Liver Transplant. Updated January 2018. Available at: https://www.niddk.nih.gov/health-information/liver-disease/liver-transplant. Accessed on June 08, 2021.**

5. **Organ Procurement and Transplantation Network. Available at: http://optn.transplant.hrsa.gov/. Accessed on June 08, 2021.**
6. **Transplant Genomics, Inc. TruGraf® Long-term Clinical Outcomes Study. NLM Identifier: NCT04491552. Last updated on April 27, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04491552?term=trugraf&draw=2&rank=1. Accessed on June 16, 2021.**

Websites for Additional Information

1. **American Society of Nephrology. Available at: https://www.asn-online.org/. Accessed on June 08, 2021.**
2. **American Society of Transplantation. Available at: https://www.myast.org/. Accessed on June 16, 2021.**
3. **American Society of Transplant Surgeons. Available at: https://asts.org/. Accessed on June 16, 2021.**
4. **United Network for Organ Sharing. Available at: http://www.unos.org/. Accessed on June 08, 2021.**

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	08/12/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.