Local Coverage Determination (LCD): MolDX: TruGraf Blood Gene Expression Test (L38135)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
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LCD Information

Document Information

LCD ID **Original Effective Date**

L38135

LCD Title
MolDX: TruGraf Blood Gene Expression Test

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL38135

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

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N/A

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01/04/2020

CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for the TruGraf Blood Gene Expression Test (Transplant Genomics Inc., Mansfield, MA) as an alternative to surveillance biopsies in kidney transplant recipients, in conjunction with standard clinical assessment.

Criteria for Coverage:

The TruGraf test is covered only when all of the following clinical conditions are met:

- Patient is at least 18 years of age.
- Recipient of a primary or subsequent deceased-donor or living-donor kidney transplantation.
- Stable serum creatinine (current serum creatinine <2.3 mg/dl, <20% increase compared to the average of the previous 3 serum creatinine levels).
- Kidney transplant patients who are more than 90 days post-transplant
- Patient is being managed in a facility that utilizes surveillance biopsies

Limitations:

TruGraf should not be used on patients who are:

- Recipients of a combined organ transplantation with an extra-renal organ and/or islet cell transplant.
- Recipients of previous non-renal solid organ and/or islet cell transplantation.

- Infected with HIV.
- Patients with BK nephropathy.
- Patients that have nephrotic proteinuria (urine protein >3 gm/day).

Summary of Evidence

Kidney transplantation is the optimal treatment for many patients with end-stage renal disease. In 2018, there were 21,167 kidney transplants performed in the U.S.[1] With the development of newer immunosuppressive drugs, more effective anti-microbial prophylaxis, and improved surgical techniques outcomes of kidney transplantation have improved in the past few decades as a result of; however, rejection is still a problem over time. Routine post-transplant monitoring consists of the measurement of serum creatinine (SCr) and immunosuppressive drug levels. Both are insensitive and non-specific markers of graft damage. As a consequence, in spite of improved short term outcomes, 10 years after transplantation roughly half of transplanted kidneys are no longer still functioning.[2]

A key problem underpinning long term graft loss relates to immune rejection of the grafted kidney, which is mitigated in part by immunosuppressive drug therapy to prevent the recipient's immune system from rejecting the kidney.[3] However, immunosuppressive drugs themselves are associated with significant side effects including the development of opportunistic infections, increased risk of certain cancers, and even direct nephrotoxicity.[3] As such, the management of a transplant recipient involves achieving the right balance between adequate immunosuppression to minimize rejection while avoiding too much immunosuppression, increasing the risk of side effects.

There are significant challenges to detecting injury early when the kidney has the greatest chance of regaining normal function. Approaches to monitoring and detecting kidney injury include intermittent measurements of serum creatinine levels[4,5], immunosuppressive drug levels[4,5,] and performing surveillance graft biopsies at some transplant centers.[6,7] Additionally, research suggests that early treatment of subclinical rejection using surveillance biopsies leads to better graft outcomes.[8] However, biopsies are invasive and themselves associated with infrequent but significant risks.[9] Additionally, at present biopsies are evaluated using the Banff criteria, which rely on visual interpretation by a pathologist, and have significant intra-observer variation in interpretation of biopsy results exists.[10]

Given that surveillance biopsies are an accepted method to look for graft rejection, a clearly treatable cause of graft injury, within the current accepted management approaches for post-renal transplant care, and biopsies are invasive and associated with risk, there is potential clinical utility for non-invasive testing that can identify graft rejection and spare a patient a biopsy. Additionally, transplant clinicians have expressed agreement that such a test could be used in the framework of existing protocols.[11]

TruGraf Test Description and Performance

The TruGraf test is a test that attempts to fill the role of minimally invasive graft status monitoring. The TruGraf test is a minimally-invasive test that measures differentially expressed genes in the blood of renal transplant recipients to identify patients who are likely to be adequately immunosuppressed. TruGraf uses DNA microarray technology to determine whether a patient's blood gene expression profile is more similar to that obtained from a reference population classified by simultaneous histological analysis of a biopsy as Transplant eXcellence (TX), and likely adequately immunosuppressed, or not-TX, and likely to be inadequately immunosuppressed.

TruGraf analytical validation data were initially published in 2017

[11] and are summarized in the table below.

General

Intended Use	The TruGraf test is intended for use in kidney transplant recipients with stable renal function as an alternative to surveillance biopsies in facilities that utilize surveillance biopsies.
Specimen Types	Plasma collected in PAXgene Blood RNA (IVD) tubes

Analytical Performance

Accuracy	PAXgene Blood RNA tubes (BD/ PreAnalytix) were obtained from a total of 295 kid recipients in 3 cohorts (126, 130 and 39 samples, respectively). These samples co reporting range and were processed through the Affymetrix GeneTitan workflow. R samples of TX and not-TX were included, as determined by paired biopsy sample h Samples were randomized to one of several arrays in order to minimize processing classification ("molecular phenotype") was compared to original histology results. I analysis was performed on the Affymetrix Expression Console software. **RESULTS**: TruGraf test accuracy was 72% (95% CI)
Minimum Input Quantity and Quality	**RESULTS**: Review of the GAPDH 3' to 5' Ratio housekeeping gene metric for samp demonstrated values ranging from 1.08 to 1.29, indicating high quality labeled RN signal intensity data for the 3'IVT Labeling and Hybridization Controls ("External R demonstrated decreased performance seen for higher input concentration for both hybridization reactions. Data from these studies, in combination with Affymetrix do us to establish RNA input conditions of 200 ng/reaction of globin-reduced RNA for t reaction and 7.5 ug/reaction of labeled cRNA for the hybridization reaction.
Limit of Detection	LOD testing was performed on a dilution series of HeLa Control RNA samples. We u of 3' IVT Labeling reaction input concentrations and 4 Hybridization reaction input Data analysis was performed on the Affymetrix Expression Console software. **RESULTS:** Review of the GAPDH 3' to 5' Ratio housekeeping gene metric for samp demonstrated values ranging from 1.08 to 1.29 indicating high quality input RNA a detectable limit of 50ng of input RNA
Linearity and Reportable Range	Linearity: NA, TruGraf is a qualitative test Reportable Range: PAXgene RNA Blood tubes were obtained from a total of 295 Tr in 3 cohorts (126, 130 and 39 samples, respectively). These samples covered the range of TX and not-TX as determined by paired biopsy sample histology, and wer through the complete Affymetrix GeneTitan workflow. TruGraf is a qualitative assa

	reports TX or not-TX. All samples generated results in the reportable range.
Precision: Repeatability Single Run, Lot, Day & Operator	Globin-reduced RNA from duplicate specimens (biological replicates) from 4 norma blood specimens was processed using the Affymetrix GeneTitan system starting at the protocol. All 8 samples were processed on a single run. In-Process QC data wa concentration, OD 260/280 ratio, RIN value and BioAnalyzer (BA) electropherogra applicable) in addition to Hyb QC data. Data analysis was performed on the Affyme Console software. **RESULTS:** Distribution statistics were analyzed and all samples demonstrated control intensities within +/- 2.5 S.D. of the mean intensities. CVs fo RNA controls were less than 10% indicating a high degree of reproducibility. Pears data was obtained and overall correlation ranged from 0.958 to 1.00 indicating the were well correlated across samples in this cohort.
Precision: Intermediate Repeatability Multiple Runs, Lots, Days and Operators	Inter-assay repeatability (between-run precision) using multiple lots of reagents ov runs. Globin-reduced RNA from duplicate specimens (biological replicates) from 4 r (NS) blood specimens was processed using the Affymetrix GeneTitan system starti step in the protocol. At least two lot numbers of GeneTitan HG-U133+ Array Strips reagents, Qiagen PAXgene RNA (IVD), and 3' IVT Plus and Hybridization/Wash/Sta used for this cohort. In-Process QC data was obtained (RNA concentration, OD 260 value and BA electropherogram data as applicable) in addition to Hyb QC data. Da performed on the Affymetrix Expression Console software. **RESULTS:** Review of in demonstrated control intensities within +/- 2.5 S.D. of mean intensities. The CVs f Controls were < 15%, with the Poly A LYS Control (present at LOQ) showing the h Poly A DAP Control (present at highest concentration) showing a CV below 10%. E hybridization RNA controls showed a CV of <5% indicating a high degree of reprod
Lot to Lot Reproducibility	Review of in-process QC data demonstrated control intensities within +/- 2.5 S.D. intensities. The CVs for the Poly A Controls were < 15%, with the Poly A LYS Contr LOQ) showing the highest CV and the Poly A DAP Control (present at highest conce showing a CV below 10%. External hybridization RNA controls showed a CV of <5% high degree of reproducibility.
Interfering Substances	RNA from the HeLa Control supplied with the 3' IVT was spiked with genomic DNA thru array Hyb on the Affymetrix GeneTitan. **RESULTS:** Review of the GAPDH 3' to 5' Ratio housekeeping gene metric for samp demonstrated values ranging from 1.13 to 1.88, indicating high quality labeled RN intensity variance, as expressed by CV%, was reviewed for TruGraf classifier – info probesets. These data indicate that 10-20% genomic DNA contamination of sample interfere with individual probeset intensity. When the percentage of contaminating reached 30% individual probeset signal intensity showed increased variance as see However, this effect of contaminating DNA was seen to have a minor impact on the intensities and no impact was seen on the final classifier results.
Specimen Stability	Review of in-process QC data enabled us to determine that samples subjected to e temperatures (> 40^{O}C) or extended periods at ambient temperatures (>3 days) pr extraction yielded degraded RNA unsuitable for downstream processing. SOP Requ received ≤3 days post blood draw.
Reagent Stability	All reagents are consumed prior to the Vendor provided expiration date or discarde that date. Standard lot-to-lot QC is performed on new reagent lots per methods de EP-26A.

Clinical Performance:

A more recent study of TruGraf's clinical performance has been demonstrated in a prospective multi-center observational study that included simultaneous blood test and clinical assessment of 192 patients across 7 transplant centers.[12] The TruGraf test result called 124 patients (65%) as TX and 68 patients (35%) as not-TX. The overall accuracy of the TruGraf blood test (concordance between TruGraf result and clinical phenotype) was 74% (142/192), and the accuracy of a TruGraf test result of TX was 94% (116/124. The false negative rate was 4%. Additional performance metrics of the TruGraf test were NPV 91%, PPV 48%, sensitivity 76% (95% Confidence Interval [CI]; CI 59-89%) and specificity 73% (95% CI; 66-80%). These diagnostic metrics were adjusted for prevalence, and the unadjusted NPV and PPV of the classifier on the EAP samples were 93% and 38% respectively, showing that adjusting for true prevalence (75% TX, 25% not-TX) did not change the NPV significantly (90%) but improved the PPV to 48%.

TX Accuracy	**94%**
Accuracy	**74%**
Sensitivity (not-TX)	**76** (95% CI 59-89%)
Specificity (TX)	**73%** (95% CI; 66-80%)
NPV	**91%**
PPV	**48%**

In this same study, physicians reported that TruGraf test results would have impacted their decision regarding patient management in 168/192 (87.5%) of cases.

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality of evidence – Moderate
Strength of evidence – Moderate
Weight of evidence – Low

There is little question that renal transplantation is able to provide patients who have renal failure in their native kidneys with a working allogeneic kidney. However, graft failure at some point tends to occur. The evidence does not support a single best management strategy post-transplant for renal allograft care, but surveillance biopsies are one post-transplant surveillance strategy to assist with allograft care and to assess for rejection used by some transplant centers. However, this requires an invasive procedure, which is itself not without risks. The TruGraf blood test allows for surveillance without a biopsy, and it has a high negative predictive value to assess for rejection. In addition, the test has evidence suggesting that practicing transplant physicians find it to be clinically useful. As such, this contractor will cover this test to be used, at the discretion of a treating physician in lieu, of surveillance biopsies for transplant centers that carry out surveillance biopsies. For patients with evidence of renal graft problems, this test is not currently indicated.

This test has shown adequate evidence that it provides incremental information which is used by clinicians to change

management so as to improve patient outcomes.

MolDX will continue to monitor the science in the transplant genomics space, with the anticipation that what is reasonable and necessary for a test such as this may change to either new evidence about the test specifically, or new evidence regarding standards of care in renal transplantation.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/05/2020	R1	The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57746 - Billing and Coding: MolDX: Trugraf Blood Gene Expression Test
A57744 - Response to Comments: MolDX: TruGraf Blood Gene Expression Test
LCD(s)
DL38135
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/29/2020 with effective dates 01/05/2020 - N/A
Updated on 11/15/2019 with effective dates 01/05/2020 - N/A

Keywords

N/A