Local Coverage Determination (LCD): MolDX: AlloSure® Donor-Derived Cell-Free DNA Test (L37303)

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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
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

LCD Information

Document Information

LCD ID **Original Effective Date**

L37303

LCD Title
MolDX: AlloSure® Donor-Derived Cell-Free DNA Test

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37303

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

For services performed on or after 12/11/2017

Revision Effective Date
For services performed on or after 11/01/2019

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
10/25/2017

Notice Period End Date
12/10/2017

CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are

considered to be reasonable and necessary.

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

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This Medicare contractor will provide limited coverage for the AlloSure donor-derived cell-free DNA test (CareDx, Inc., Brisbane, CA) to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of renal biopsy in such patients at least 2 weeks post-transplant in conjunction with standard clinical assessment.

Summary of Evidence

Kidney transplant is the preferred treatment for patients with end-stage renal disease, offering superior survival, quality of life, and cost savings compared to dialysis. There are approximately 18,000 new renal allograft recipients each year and 200,000 living renal transplant recipients.[1] Major advances in the past two decades have reduced acute rejection and increased short-term graft survival but these have not been matched by improvement in long term allograft and patient survival, which remain largely unchanged.[2] Renal transplants fail in approximately 20% of kidney transplants by 5 years, and the mortality rate in this population is approximately 37%. A high percentage of renal recipients younger than 50 years of age will require a second (or even third) kidney transplant.[3] Further, the overall cost of care for a Medicare beneficiary whose renal transplant failed was 500% more than a beneficiary with a functioning transplant.[4]

A significant challenge in the management of kidney transplant patients is the poor sensitivity and specificity of tests or procedures for immune monitoring and graft function.[5] The AlloSure test for donor-derived cell-free DNA (dd-cfDNA) detected in the blood of transplant recipients has been developed as a noninvasive marker for diagnosis of graft rejection.[6] The premise for AlloSure is that rejection entails injury, including increased cell death in the allograft, leading to increased dd-cfDNA released into the bloodstream.

AlloSure Donor-derived Cell-free DNA Test Description and Performance

The AlloSure assay is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to accurately quantify dd-cfDNA in transplant recipients without separate genotyping of donor or recipient.[7] The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs and can be completed within 3 days of peripheral blood collection, a practical turnaround time for management of transplant recipients. AlloSure assay results are reported as the percentage of dd-cfDNA in total cfDNA.

The clinical performance of AlloSure in kidney transplantation has been demonstrated in a prospective multicenter observational study (Diagnosing Active Rejection in Kidney Transplant Recipients, or DART) that included 102 patients and 107 samples.[6,8] The dd-cfDNA level discriminated between patients with biopsy specimens showing any rejection (defined as T cell-mediated rejection [TCMR] or antibody-mediated rejection [ABMR]) versus no rejection histologically, $P<0.001$ for a Wilcoxon non-parametric test between groups). The area under the receiver operating characteristic curve [AUROC or AUC] was 0.74 (95% CI 0.61 to 0.86). In this study in which the prevalence of any

rejection was approximately 26%, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for active rejection were 59.3%, 84.7%, 60.6% and 84.0%, respectively, using a method that accounts for multiple samples from the same patient. (Limiting the analysis to unique patients, the corresponding figures are 59.3%, 84.0%, 57.1% and 85.1%, respectively.) The AUC for discriminating ABMR from samples without ABMR was 0.87 (95%CI, 0.75 to 0.97). The PPV and NPV for ABMR at a cutoff of 1.0% dd-cfDNA were 44.4% and 96.4%, respectively.

The analytical and clinical performance of the AlloSure assay is summarized below.

General

Intended Use	The AlloSure test is intended to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of renal biopsy in such patients at least 2 weeks post-transplant in conjunction with standard clinical assessment.
Specimen Types	Plasma collected in Streck Cell-Free DNA BCT® tubes

Analytical Performance

Description	**Results**			
Accuracy				
Assessed across seven "donor'/'recipient" gDNA mixtures (contrived specimens made from cell lines, range 0.25%-16%, sonicated to 160 bp fragments to mimic cfDNA) in three different panels. Each mixture in each panel was run in 12 replicates each for 3ng and 8ng total cfDNA input mass. The slope, intercept, and correlation between digital PCR results on the tracker gene (EGFR T790M) and AlloSure results were determined for the set of 7 mixtures.			Average	95% CI
	3ng	Slope	1.23	1.19-1.27
		Intercept	-0.0009	-0.0016 to -0.0002
		R2	0.997	0.996-0.999
	8ng	Slope	1.28	1.25-1.30
		Intercept	-0.0008	-0.0011 to -0.0006
		R2	0.998	0.998-0.999
Intermediate precision (inter-assay total variability)				
Contrived specimens (described above): Twelve replicate runs performed on 12 separate days by four operators using two Fluidigm Access Array systems, four Illumina MiSeq sequencing instruments, 2 manufacturing lots of Access Array chips and 8 lots of sequencing kits. One lot of critical raw reagents was used.	Quantitative: Mean CV across dd-cfDNA levels = 6.8% at 8 ng input mass (covers 83% of the population), 9.9% at 3 ng input mass (covers 99% of the population) Qualitative: 100% concordance (95% CI: 90.5-100%) between replicate specimens for 37 patient visits			

Patient specimens: 37 samples; 26 "no rejection" (dd-cfDNA range 0-0.94%); 11 "active rejection" (dd-cfDNA range 1.32-13.05%). Two replicate runs performed for each paired tubes of specimens from the same venipuncture. In total, these were run by 5 operators across 21 separate days using two Fluidigm Access Array systems, four Illumina MiSeq sequencing instruments, 3 manufacturing lots of Access Array chips and 7 lots of sequencing kits. 1-2 lots of critical raw reagents were used.	
Sensitivity-minimum input	3 ng total cfDNA input mass statistically inferred from variability in sequencing read coverage across 266 SNPs and the fraction of recipient homozygous SNPs
Limit of Detection Determined separately for different degrees of relationship between donor and recipients.	At 3 ng input cfDNA Unrelated: 0.19% dd-cfDNA Closely related[1]: 0.28% dd-cfDNA Sibling, parent, child, grandparent, grandchild, aunt, uncle, half-sibling[1]
Lower Limit of Quantitation Determined separately for different degrees of relationship between donor and recipients based on a CV < 20%.	0.37% dd-cfDNA for all relationship classes at 3 ng input cfDNA
Upper Limit of Quantitation Determined separately for different degrees of relationship between donor and recipients based on a CV < 20%.	16% for all relationship classes at 3 ng input cfDNA
Reference Range Established in 380 samples from 93 stable kidney transplant recipients from DART (i.e., excluding patients with impaired or unstable renal function or other clinical complications).	0-1.0% (1.0% is the 96th percentile; 1.2% is the 97.5th percentile).
Interfering substances Interferent diluents were added to 2.0% spike-ins of donor to recipient cfDNA from healthy volunteers. Acceptance criteria were ± 0.2% dd-cfDNA.	Interference was observed with 2.0 mg/dL hemoglobin, but not with 20 mg/dL (342 µmol/L) bilirubin and 37 mmol/L triglycerides. Hemolyzed samples (as assessed by a visual scale) are currently excluded.
Critical reagent shelf-life and (as applicable) open stability	For the 4 critical reagents (2x Phusion Flash master mix, Phusion Hot Start II DNA polymerase kit, Fast Start High Fidelity PCR kit, and Allosure SNP primers), manufacturer stability claims are used and monitored by in-run controls.

Specimen stability: Primary sample	Per the manufacturer, whole blood collected in Streck Cell-Free DNA BCT is stable for 7 days at room temperature. cfDNA in plasma and post-extraction buffer: 3 months at -80°C based on concordant AlloSure results (see Intermediate precision, patient specimens above)
Specimen stability: Intermediate	Stability at all other intermediate storage points (i.e., completion of pre-amplification; completion of pre-amplification; completion of the exonuclease step; completion of Access Array targeted amplification; completion of barcoding; and completion of library pooling and clean-up) was not empirically determined, but storage at -20°C based on literature and monitored by in-run controls.

Clinical Performance: Validity

Description	**Results (with 95% Confidence Intervals if applicable)***	
	Active vs No Rejection**	ABMR vs no ABMR
Sensitivity	59% (44-74%)	81% (67-100%)
Specificity	85% (79-91%)	83% (78-89%)
NPV	84% (79-89%)	96% (94-100%)
PPV	61% (50-73%)	44% (36-57%)

* All metrics based on dd-cfDNA threshold for rejection at > 1.0%.

** As published 6, using a method that accounts for multiple samples from the same patient. Analysis limited to unique patients yields very similar results: 59% (39-78%) sensitivity, 84% (74-91%) specificity, 85% (75-92%) NPV and 57% (37-76%) PPV.

The DART study suggests that use of AlloSure may reduce invasive percutaneous renal biopsy procedures among patients with risk of rejection.[6] Seventy-four percent of clinically indicated biopsies (based on elevated creatinine levels) did not ultimately get a histopathological diagnosis of rejection, thereby unnecessarily exposing recipients to risk of complications from invasive biopsies. Based on the rate of AlloSure scores ≤1% in the DART study, approximately 72% of clinically indicated biopsies (usually based on elevated creatinine levels) may have been avoided if providers strictly adhered to ≤1% cutoff for rejection.

Criteria for Coverage

The AlloSure assay is covered only when the following clinical conditions are met:

- Renal allograft recipients > 18 years
- Physician-assessed pretest need to further assess patient for the probability of active renal allograft rejection
- At least 2 weeks post-transplant

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality of evidence – Moderate

Strength of evidence – Limited

Weight of evidence - Limited

This contractor recognizes that the evidence of clinical utility for the use of AlloSure in its intended use population is promising at the current time. However, this contractor believes that forthcoming prospective clinical studies will demonstrate improved patient outcomes. Continued coverage for AlloSure testing is dependent on annual review by this contractor of such data and publications.

Data collected by CareDx through such current and future studies will include at least the following:

- The pre-test biopsy recommendation by the provider
- The AlloSure result (%dd-cfDNA) at the time of each biopsy
- The post-test biopsy decision by the patient
- The frequency of renal biopsies in transplant patients managed with and without AlloSure testing
- The sensitivity, specificity, PPV and NPV of AlloSure for active rejection, TCMR and ABMR
- The incidence of interstitial fibrosis, tubular atrophy and transplant glomerulopathy within the first year post-transplant in patients managed with and without AlloSure testing, as determined by central pathology review
- For any histopathological diagnosis of rejection, the grade

This additional data is expected to establish the clinical utility of AlloSure by identifying renal transplant recipients who may use AlloSure testing in the first year post transplant to safely avoid unnecessary procedures and/or interventions.

General Information

Associated Information

N/A

Sources of Information

N/A

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8. Bromberg JS, Brennan DC, Poggio E, et al. Biological variation of donor-derived cell-free DNA in renal transplant recipients: clinical implications. J Appl Lab Med. 2017; doi: 10.1373/jalm.2016.022731.

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
11/01/2019	R2	11/01/2019: This LCD is being revised in order to adhere to CMS requirements per chapter 13, section 13.5.1 of the Program Integrity Manual. There has been no change in coverage with this LCD revision. Regulations regarding billing and coding were removed from the **CMS National Coverage Policy** section of this LCD and placed in the related Billing and Coding: AlloSure® Donor-Derived Cell-Free DNA Test Article A57456.	• Provider Education/Guidance
11/01/2019	R1	As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.	• Revisions Due To Code Removal

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A57456 - Billing and Coding: MolDX: AlloSure® Donor-Derived Cell-Free DNA Test

A55760 - Response to Comments: MolDX: AlloSure® Donor-Derived Cell-Free DNA Test

LCD(s)
DL37303
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/28/2020 with effective dates 11/01/2019 - N/A
Updated on 10/07/2019 with effective dates 11/01/2019 - N/A
Updated on 10/11/2017 with effective dates 12/11/2017 - N/A

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