Local Coverage Determination (LCD): MolDX: AlloSure® or Equivalent Cell-Free DNA Testing for Kidney and Heart Allografts (L38355)

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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
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Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
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LCD Information

Document Information

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MolDX: AlloSure® or Equivalent Cell-Free DNA Testing for Kidney and Heart Allografts

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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.

CMS Internet-Only Manuals, Pub. 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 tests performed using the AlloSure® donor-derived cell-free DNA assay (CareDx®Inc., Brisbane, CA) for the following indications:

1. AlloSure® Kidney is covered 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.

AlloSure® Heart is covered when used in conjunction with AlloMap® to assess the probability of allograft rejection in heart transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of a heart biopsy in such patients at least 55 days post-transplant in conjunction with standard clinical assessment.

Other tests that demonstrate similar indicated uses and similar performance to AlloSure®, as demonstrated in a technical assessment, may similarly be covered under this policy.

Summary of Evidence

For many patients with end stage renal or heart disease, allograft transplantation is the definitive treatment. In 2018, there were 21,167 kidney transplants and 3,408 heart transplants in addition to 836 kidney/pancreas transplants and 32 heart/lung transplants.[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]

The importance of graft rejection and immunosuppression was discovered early on following the development of transplantation, a challenge that started to be overcome with the availability of immunosuppressants.[3-5] Over the ensuing years, there has been a steady rise in the 1 year survival and overall median duration of survival following a heart transplant, which has been attributed in part to immunosuppressive therapy, but challenges related to immunosuppression still remain one of the key factors limiting long term survival in cardiac transplant recipients and long term outcomes of renal allografts, which have a failure rate of 20-30% within the first 5 years. [3,4,6-8] The management of immunosuppression has a number of challenges, since inadequate immunosuppression may lead to rejection, but immunosuppressive treatment itself is associated with other serious health problems including infection and renal insufficiency.[8] Graft assessment is used clinically to assist in the management of immunosuppression; the clinical value it brings is that it allows modification of immunosuppressive therapy so as to maximize graft longevity, which is a focus of post-transplant care.

Histology has traditionally been used, potentially in conjunction with serologic markers as a common graft assessment tool.[6,7,9-13] While histology is considered the gold standard of diagnosis at this point in time, this requires a biopsy, which is invasive and may be associated with significant risks and access to care barriers. Additionally, timely detection of graft rejection is associated with a significant improvement in allograft survival.[14]

Collectively, this indicates that a test that is able to provide information that will help to inform immunosuppression and rejection management while avoiding an invasive procedure and potentially expanding access to care has clinical utility.

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

The premise for AlloSure® is that rejection entails injury, including increased cell death in the allograft, leading to increased donor-derived cell-free DNA (dd-cfDNA) released into the bloodstream.[15] The AlloSure® test for dd-cfDNA detected in the blood of transplant recipients has been developed as a noninvasive marker for diagnosis of graft rejection.[15] 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 analytical performance of AlloSure® was published in a study by Grskovic et al[16] and is summarized in the table below.

Analytical Performance

Description	**Results**			
Accuracy			Average	95% CI
Assessed across 7 "donor'/'recipient" gDNA mixtures (contrived specimens made from cell lines, range 0.25%-16%, sonicated to 160 bp fragments to mimic cfDNA) in 3 different panels. Each mixture in each	3ng	Slope	1.23	1.19-1.27
		Intercept	-0.0009	-0.0016 to -0.0002
		R2	0.997	0.996-

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.	8ng	Slope	1.28	0.999 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): 12 replicate runs performed on 12 separate days by 4 operators using 2 Fluidigm Access Array systems, 4 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. 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 2 Fluidigm Access Array systems, 4 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.

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

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

16% for all relationship classes at 3 ng input cfDNA

Determined separately for different degrees of relationship between donor and recipients based on a CV < 20%.	
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 of AlloSure® kidney

Description	**Results (with 95% Confidence Intervals if applicable)***

	Active vs No Rejection**	ABMR vs no ABMR
Sensitivity	59%	81%
Specificity	85%	83%
NPV	84%	96%
PPV	61%	44%

All metrics based on dd-cfDNA threshold for rejection at > 1.0%. As published in the DART study, using a method that accounts for multiple samples from the same patient.

Clinical Performance: Validity of AlloSure® Heart

Description	**All Samples**	**Surveillance Biopsies***	**For-cause Biopsies***
AUC	64%	60.50%	68.50%
Specificity	80%	84%	76.10%
Sensitivity	44%	38.10%	53.80%
PPV	8.90%	8.10%	11.60%
NPV	97.10%	97.30%	96.60%

All metrics based on dd-cfDNA threshold for rejection at > 0.2%. Data from the D-OAR study

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.[15,17] 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. 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 DART study suggests that use of AlloSure® may reduce invasive percutaneous renal biopsy procedures among patients with risk of rejection.[15] 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.

The clinical performance of AlloSure® in heart transplantation has been demonstrated in a prospective multicenter observational registry study, the Donor-Derived Cell-Free DNA-Outcomes

AlloMap® Registry (D-OAR) study[16] included 841 samples paired with biopsy tissue from 443 patients. These

included both surveillance and for-cause biopsies. Patients with rejection had both antibody mediated (n=18) and acute cellular rejection (n=17). The dd-cfDNA level discriminated between patients with biopsy specimens showing any rejection versus no rejection histologically (P = 0.005 for a Wilcoxon non-parametric test between groups). The area under the receiver operating characteristic curve [AUROC or AUC] was 0.64. In this study in which the prevalence of any rejection was approximately 4% (35 out of 841 samples), the sensitivity, specificity, PPV and NPV for active rejection were 44%, 80.0%, 8.9% and 97.1%, respectively.

A separate test using Gene-Expression Profiling, AlloMap® is marketed by CareDx® for cardiac transplantation and has been covered under the MolDX program as a non-invasive means to assess allograft rejection status. Following this initial decision, additional data has been published, including a registry study of 1,499 patients from the OAR registry.[18] AlloMap® was found to have sensitivities, specificities, PPV, and NPV for rejection at various time points as described in the table below. AlloMap® has been characterized as a "rule-out" test for rejection that can be complemented by a cell-free DNA "rule-in" test.[19] The utility of the combination of these 2 tests when used together was assessed as part of the CARGO II study,[20] in a separately presented sub-analysis, the combination of these 2 scores resulted in an area under the curve of 0.78[21], suggesting that together these tests enhance the accuracy of assessing rejection status than either test alone.

AlloMap® clinical performance

Time post-transplant	Gene Expression Score Nominal Threshold	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
2-6 months	30	2.83	98.44	50	64.3
> 60 months	34	2.82	98.5	51.1	63.4

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality of evidence – Moderate
Strength of evidence – Limited
Weight of evidence - Moderate

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury[22] where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.[23] The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health

outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

It is well accepted within the renal and cardiac transplant communities that immunosuppression management is an important component of post-transplant care to both optimize graft longevity while avoiding side effects and toxicity of immunosuppressive therapies. Graft assessment is an important decision tool used to help clinicians optimize immunosuppressive treatment. The gold standard for assessing rejection or a solid organ allograft rejection or injury has historically and remains a biopsy in conjunction with serologic criteria. However, given the invasive nature and risks associated with a biopsy, tests that can potentially mitigate the need for a biopsy while still providing clinicians with actionable information that can be used to help optimize immunosuppressive therapy are reasonable and necessary. Thus there is adequate evidence to support that the AlloSure® assay when used in combination provides incremental information to change clinician management in a way that will be expected to improve outcomes.

Non-invasive graft assessment remains an actively evolving area of medicine. As such, this contractor will continue to monitor the evidence, and new developments may impact this coverage decision.

General Information

Associated Information

N/A

Sources of Information

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A57380 - Billing and Coding: MolDX: AlloSure® or Equivalent Cell-Free DNA Testing for Kidney and Heart Allografts

A58481 - Response to Comments: MolDX: AlloSure® or Equivalent Cell-Free DNA Testing for Kidney and Heart Allografts

LCD(s)

DL38355 - MolDX: AlloSure® Cell-Free DNA Testing

Related National Coverage Documents

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