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

Noridian Healthcare Solutions, LLC

Please Note: This is a Proposed LCD.
Proposed LCDs are works in progress and not necessarily a reflection of the current policies or practices. Proposed LCDs in an approval status display on the CMS MCD for public review.

Contractor Information

Proposed

Contractor Name: Noridian Healthcare Solutions, LLC
Contract Number: 03102
Contract Type: A and B MAC

Associated Contract Numbers:

Proposed LCD Information
Proposed LCD ID
DL37358

Proposed LCD Version
3

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

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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.

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.


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

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes".

Jurisdiction
Arizona
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.

**Background**

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. 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. 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. Further, the overall cost of care for a Medicare beneficiary whose renal transplant failed was 500% more than a beneficiary with a functioning transplant.

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. 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. 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. 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**

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessed across seven &quot;donor/recipient&quot; gDNA mixtures (contrived specimens made from cell lines, range 0.25%-16%, sonicated to 160 bp fragments to mimic cfDNA) in</strong></td>
<td><strong>Average 95% CI</strong></td>
</tr>
<tr>
<td><strong>Slope</strong></td>
<td>1.23</td>
</tr>
<tr>
<td><strong>3ng Intercept</strong></td>
<td>-0.0009</td>
</tr>
<tr>
<td><strong>R2</strong></td>
<td>0.997</td>
</tr>
<tr>
<td><strong>8ng Slope</strong></td>
<td>1.28</td>
</tr>
<tr>
<td><strong>8ng Intercept</strong></td>
<td>-0.0008</td>
</tr>
</tbody>
</table>
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.

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.

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

R2 0.998 0.998 - 0.999

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

3 ng total cfDNA input mass statistically inferred from variability in sequencing read
coverage across 266 SNPs and the fraction of recipient homozygous SNPs
At 3 ng input cfDNA
Unrelated: 0.19% dd-cfDNA
Closely related1: 0.28% dd-cfDNA

1Sibling, parent, child, grandparent, grandchild, aunt, uncle, half-sibling

Limit of Detection
Determined separately for different degrees of relationship between donor and recipients.

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 Allsoure 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.

Specimen stability: Intermediate
cfDNA in plasma and post-extraction buffer: 3 months at -80°C based on
concordant AlloSure results (see Intermediate precision, patient specimens above)

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

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

* 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

This contractor recognizes that the evidence of clinical utility for the use of AlloSure in its intended use population is limited at the current time. However, this contractor believes that forthcoming prospective clinical studies in these patients 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.

Proposed Process Information
# Proposed

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<th>Synopsis of Changes</th>
<th>Changes</th>
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## Associated Information

## References


### Open Meetings

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<tr>
<th>Meeting Date</th>
<th>Meeting Information</th>
<th>State</th>
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### Part B MAC Contractor Advisory Committee (CAC) Meetings

<table>
<thead>
<tr>
<th>Meeting Date</th>
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### Comment Period

- **Start Date**: 06/01/2017
- **End Date**: 08/14/2017
- **Released to Final LCD Date**: Not yet released.
- **Reason(s) for Proposed LCD**: Creation of Uniform LCDs With Other MAC Jurisdiction

### Proposed LCD Contact

Noridian Healthcare Solutions, LLC JF Part A Contractor Medical Director (s)

Attention: Draft LCD Comments

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Fargo, North Dakota 58108-6781

policydraft@noridian.com

### Coding Information

#### Bill Type Codes

#### Revenue Codes
CPT/HCPCS Codes

Does the CPT 30% Coding Rule Apply?

No

ICD-10 Codes that Support Medical Necessity

Note: Performance is optimized by using code ranges.

ICD-10 Codes that DO NOT Support Medical Necessity

Note: Performance is optimized by using code ranges.

Additional ICD-10 Information

Associated Documents

Attachments

There are no attachments for this LCD.

Related Local Coverage Documents

This LCD version has no Related Local Coverage Documents.

Related National Coverage Documents

This LCD version has no Related National Coverage Documents.