

# Molecular Diagnostic Assays and Breath Testing for Transplant Rejection



INDEPENDENT CARE HEALTH PLAN

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## Medicare Advantage Medical Coverage Policy

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#### Disclaimer

The Coverage Summaries are reviewed by the iCare Medicare Utilization Management Committee. Policies in this document may be modified by a member's coverage document. Clinical policy is not intended to preempt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. References to CPT® codes or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee of claims payment. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any shape or form or by any means, electronic, mechanical, photocopying or otherwise, without permission from iCare.

## Related Medicare Advantage Medical/Pharmacy Coverage Policies

None

## Related Documents

Please refer to [CMS website](#) for the most current applicable National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

## Molecular Diagnostic Assays and Breath Testing for Transplant Rejection

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
NCD	Heartsbreath Test for Heart Transplant Rejection	<a href="#"><u>260.10</u></a>		
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT)  Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)  MolDX: Molecular Testing for Solid Organ Allograft Rejection  Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection	<a href="#"><u>L36807</u></a>  <a href="#"><u>A57772</u></a>  <a href="#"><u>L38680</u></a>  <a href="#"><u>A58207</u></a>	J5 – J8 Wisconsin Physicians Service Insurance Corporation	IA, IN, KS, MI, MO, NE
LCD LCA	MolDX: Molecular Testing for Solid Organ Allograft Rejection  Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection  MolDX: Molecular Diagnostic Tests (MDT)	<a href="#"><u>L38582</u></a>  <a href="#"><u>A58061</u></a>  <a href="#"><u>L36021</u></a>	J15 - CGS Administrators, LLC (Part A/B MAC)	KY, OH
LCD LCA	MolDX: Molecular Testing for Solid Organ Allograft Rejection  Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection  MolDX: Molecular Diagnostic Tests (MDT)  Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	<a href="#"><u>L38629</u></a>  <a href="#"><u>A58168</u></a>  <a href="#"><u>L35160</u></a>  <a href="#"><u>A57526</u></a>	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands

<p>LCD LCA</p>	<p>MolDX: Molecular Diagnostic Tests (MDT)</p> <p>Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)</p> <p>MolDX: Molecular Testing for Solid Organ Allograft Rejection</p> <p>Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection</p>	<p><a href="#">L36256</a></p> <p><a href="#">A57527</a></p> <p><a href="#">L38671</a></p> <p><a href="#">A58170</a></p>	<p>JF - Noridian Healthcare Solutions, LLC</p>	<p>AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY</p>
<p>LCD LCA</p>	<p>MolDX: Molecular Diagnostic Tests (MDT)</p> <p>Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)</p> <p>MolDX: Molecular Testing for Solid Organ Allograft Rejection</p> <p>Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection</p>	<p><a href="#">L35025</a></p> <p><a href="#">A56853</a></p> <p><a href="#">L38568</a></p> <p><a href="#">A58019</a></p>	<p>JJ - Palmetto GBA (Part A/B MAC)</p> <p>JM - Palmetto GBA (Part A/B MAC)</p>	<p>AL, GANC, SC, TN, VA, WV</p>

**Description**

A biopsy is considered the gold standard for the diagnosis of organ transplant rejection. There are no specific laboratory findings that can accurately diagnose acute rejection. Organ biopsy is required to differentiate between T-cell mediated rejection (TCMR) and antibody mediated rejection (ABMR), to accurately grade the severity of rejection, and to determine the degree of organ damage. Biopsy of the allograft organ can also reveal other causes of inflammation and injury. Noninvasive methods for the detection and surveillance of transplant rejection have been developed with the goal of reducing the number of biopsies. These tests include, but may not be limited to, the following:

**Gene Expression Profiling**

- A **gene expression test** (eg, **AlloMap**) has been developed to predict the likelihood of cardiac rejection. Following a transplant, the test evaluates the quantitative measure of 20 genes using an algorithm to report a rejection risk score. The test is intended to be used in conjunction with standard clinical

assessment to aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection at the time of testing.<sup>33</sup>

- **Immune response gene expression panel** (eg, **nCounter Human Organ Transplant Panel**) has been developed to assess immune response following organ transplant utilizing a panel of 770 genes across 37 pathways that purportedly evaluates kidney, heart, liver and lung rejection.
- **Messenger deoxyribonucleic acid (mDNA) and Messenger ribonucleic acid (mRNA) gene expression** utilize proprietary microarrays and algorithms based on a reference set of biopsies to provide scores to assess the probability of rejection by reportedly measuring cell-mediated rejection. The tests are purportedly utilized for heart, kidney and lung transplants. Examples of mDNA and mRNA gene expression assays include, but may not be limited to:
  - **Clarava pretransplant mRNA expression assay**
  - **Molecular Microscope Diagnostic system** (eg, **MMDx Heart, MMDx Kidney, MMDx Lung**)
  - **TruGraf Blood Gene Expression Test**
  - **Tutivia post-transplant mRNA expression assay**
- **Molecular gene expression assay** (eg, **Kidney Solid Organ Response Test [kSORT]**) has been developed for kidney transplant rejection to reportedly detect individuals who are at high risk for acute rejection. Polymerase chain reaction (PCR) is utilized to measure the relative messenger ribonucleic acid (mRNA) expression levels of 17 genes that have been known to be associated with acute rejection. Individuals are classified into high, low or indeterminate risk according to a correlation-based algorithm.<sup>27</sup>

### Antigen-Specific T-cell Function Assay

- **CD154+-T-cytotoxic memory cell testing** has been developed to reportedly determine the likelihood of acute cellular rejection (ACR) by measuring the immune response of recipient lymphocytes to donor or donor-like cells. This testing is designed for determining rejection risk in renal transplants (eg, **Pleximark Tx**).

### Breath Testing

- **Breath methylated alkane contour (BMAC)** (eg, **Heartsbreath**) is a test that is purportedly indicated for use as an aid in the diagnosis of [grade 3 heart transplant rejection](#) in an individual who has received a heart transplant within the preceding year. It is intended to be used as an adjunct to, and not as a substitute for an endomyocardial biopsy. The use of the test is limited to individuals who have had an endomyocardial biopsy within the previous month.<sup>34</sup>

### Combined Gene Expression Profiling and Donor-Derived Cell-Free (dd-cfDNA) tests

- These tests are designed to reportedly provide a broad assessment of immune quiescence (inactivity) and graft injury by combining a gene expression profiling test and a dd-cfDNA test (eg, **AlloMap and AlloSure Heart [HeartCare], TruGraf and Viracor TRAC Kidney [OmniGraf]**).

### dd-cfDNA

- **Biomarker blood tests** purportedly determine allograft injury by measuring DNA fragments that are supposedly released into the bloodstream from the injured donor allograft cells. The goal of these tests is to predict active rejection using these measurements. An increase in the percentage of donor-derived cell-free DNA (dd-CF DNA) in the blood indicates injury to the transplanted (ie, donor) organ that may be caused by ACR or AMR, as well as other forms of injury. These tests include, but may not be limited to:
  - **AlloSure Heart**
  - **AlloSure Kidney**
  - **AlloSure Lung**
  - **Prospera Heart**
  - **Prospera Kidney with Quantification**
  - **Viracor TRAC (heart, kidney, liver and lung)**

### Urine-Based Tests for Allograft Rejection

Several urine-based tests have been proposed utilizing various biomarkers to aid in the diagnosis of acute rejection in kidney transplant recipients. Purportedly, the tests measure urine mRNA, urine proteins and/or urine proteomics. Some tests measure several biomarkers (eg, **QiSant [also known as QSant]**) to reportedly determine acute kidney transplant rejection. The biomarkers include, but may not be limited to, cfDNA, methylated cfDNA, clusterin, CXCL10, creatinine and total protein, which are integrated into an algorithm to supposedly determine kidney risk rejection scores.

## Coverage Determination

*iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.*

*Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.*

*For jurisdictions with no Medicare guidance, iCare will utilize the [MolDX program](#) and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.*

*In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the following criteria:*

The following tests will be considered reasonable and medically necessary in lieu of a biopsy, for post-transplant surveillance when the following requirements are met:

**Heart**

<b><u>Test</u></b>	<b><u>Indication(s)/Criteria</u></b>
<b>AlloMap</b>	<ul style="list-style-type: none"> <li>• Absence of <a href="#">contraindications/limitations for AlloMap testing</a>; <b>AND</b></li> <li>• Individual must be a heart transplant recipient who has a low risk of moderate or severe ACR at the time of testing; <b>AND</b></li> <li>• At least 2 months (greater than or equal to 55 days) post-transplant</li> </ul>
<b>AlloSure Heart</b>	<ul style="list-style-type: none"> <li>• Absence of <a href="#">contraindications/limitations for AlloSure Heart testing</a>; <b>AND</b></li> <li>• Individual is at least 2 months (greater than or equal to 55 days) since transplantation; <b>AND</b></li> <li>• Receiving a concomitant AlloMap test</li> </ul>
<b>HeartCare</b>	<ul style="list-style-type: none"> <li>• Absence of <a href="#">contraindications/limitations for HeartCare testing</a>; <b>AND</b></li> <li>• Individual must be a heart transplant between 2 months (greater than or equal to 55 days) and 12 months post-transplant</li> </ul>

**Kidney**

<b><u>Test</u></b>	<b><u>Indication(s)/Criteria</u></b>
<b>AlloSure Kidney</b>	<ul style="list-style-type: none"> <li>• Absence of <a href="#">contraindications/limitations for AlloSure Kidney testing</a>; <b>AND</b></li> <li>• At least 2 weeks (14 days) post-transplant</li> </ul>
<b>Prospera - Kidney</b>	Covered for surveillance and cause
<b>QSant</b>	Covered for evaluation and management of kidney injury and acute rejection post-transplant
<b>TruGraf Kidney</b>	Covered for Surveillance

**Lung**

<u>Test</u>	<u>Indication(s)/Criteria</u>
<b>AlloSure Lung</b>	<ul style="list-style-type: none"> <li>• Absence of <a href="#">contraindications/limitations for AlloSure Lung testing</a>; <b>AND</b></li> <li>• For ongoing surveillance in lieu of biopsy in bilateral lung transplant individuals, who are greater than 14 days post-transplant.</li> </ul>
<b>Prospera Lung</b>	<ul style="list-style-type: none"> <li>• For ongoing surveillance in lieu of biopsy to detect lung allograft injury and rejection.</li> </ul>

*The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.*

## Coverage Limitations

[US Government Publishing Office. Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage](#)

The following **gene expression profiling for transplant rejection test** will not be considered medically reasonable and necessary:

- AlloMap Kidney
- Clarava
- Heartsbreath - *Please refer to the above Medicare guidance*
- KidneyCare
- kSORT
- MMDx Heart
- MMDx Kidney
- MMDx Lung
- nCounter Organ Transplant Panel
- OmniGraf
- Pleximark Tx
- Prospera Heart
- TruGraf Liver
- Tutivia
- Viracor TRAC Heart
- Viracor TRAC Liver
- Viracor TRAC Lung

<u>Test</u>	<u>Contraindications/Limitations</u>
<b><u>AlloMap</u></b>	<ul style="list-style-type: none"> <li>• Less than 30 days after a blood transfusion that contains white blood cells (leukocyte-depleted red blood cell transfusion is acceptable); <b>AND</b></li> <li>• Corticosteroid dosage &gt;20 mg/day: systemic corticosteroid dosage of &gt;20 mg/day of prednisone or equivalent may result in a decreased AlloMap score; <b>AND</b></li> <li>• 21 days following rejection therapy with steroids: AlloMap performance characteristics have not been established for individuals who have received rejection therapy in the 21 days prior to testing</li> </ul>
<b><u>AlloSure Heart</u></b>	<ul style="list-style-type: none"> <li>• Recipients of multiple transplanted organs originated from the same donor; <b>AND</b></li> <li>• Recipients of a bone marrow transplant; <b>AND</b></li> <li>• Recipients who are pregnant; <b>AND</b></li> <li>• Less than 24 hours following an endomyocardial biopsy</li> </ul>
<b><u>HeartCare</u></b>	Until definitive studies are completed, HeartCare should not be performed on individuals within 24 hours following an endomyocardial biopsy

<u>Test</u>	<u>Contraindications/Limitations</u>
<b><u>AlloSure Kidney</u></b>	<ul style="list-style-type: none"> <li>• Recipients of transplanted organs other than kidney; <b>AND</b></li> <li>• Recipients of a transplant from a monozygotic (identical) twin; <b>AND</b></li> <li>• Recipients of a bone marrow transplant; <b>AND</b></li> <li>• Recipients who are pregnant; <b>AND</b></li> <li>• Recipients who are less than 14 days post-transplant</li> </ul> <p>LIMITATIONS</p> <ul style="list-style-type: none"> <li>• 30 days after a blood transfusion that contains white blood cells (washed or leukocyte-depleted RBCs are acceptable)</li> <li>• 24 hours following a biopsy</li> </ul>

<u>Test</u>	<u>Contraindications/Limitations</u>
<b><u>AlloSure Lung</u></b>	• Recipients of transplanted multi organs



Test	Contraindications/Limitations
	<ul style="list-style-type: none"> <li>• Recipients of a transplant from a monozygotic (identical) twin</li> <li>• Recipients of a bone marrow / hematopoietic transplant</li> <li>• Recipients who are pregnant</li> </ul> <p>LIMITATIONS</p> <ul style="list-style-type: none"> <li>• Following blood transfusion that contains white blood cells for 30 days (washed or leukocyte-depleted RBCs are acceptable).</li> <li>• AlloSure Lung does not provide information on specific allograft histomorphology. All AlloSure Lung results must be considered in the context of an individual’s overall clinical presentation, including other diagnostic findings, history, and examination of the individual. There may be differences both within and between individuals in biological variability of baseline values of dd-cfDNA. Damage to the graft caused by invasive procedures such as trans-bronchial lung biopsy may cause a short-term elevation of dd-cfDNA. Until definitive studies are completed, AlloSure Lung should not be performed on individuals within 24h following a trans-bronchial lung biopsy.</li> </ul>

### Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81370	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1	
81371	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)	
81372	HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)	
81373	HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each	
81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1	
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1	

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81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)	
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each	
81479	Unlisted molecular pathology procedure	
81560	Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score	
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score	
81599	Unlisted multianalyte assay with algorithmic analysis	
84999	Unlisted chemistry procedure	
86849	Unlisted immunology procedure	
0018M	Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score	
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma	
0087U	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score	
0088U	Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection	
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA	
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection	
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection	

CPT® Category III Code(s)	Description	Comments
No code(s) identified		
HCPCS Code(s)	Description	Comments
No code(s) identified		

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International Society for Heart and Lung Transplantation (ISHLT) System for Grading Rejection<sup>23</sup>:

<b>Grade 0R</b>	No rejection	No interstitial cellular infiltrates
<b>Grade 1R</b>	Mild rejection	Interstitial and/or perivascular cellular infiltrate with less than or equal to one focus of myocyte damage
<b>Grade 2R</b>	Moderate rejection	Greater than or equal to two foci of cellular infiltrate with associated myocyte damage
<b>Grade 3R</b>	Severe rejection	Diffuse cellular infiltrate with multifocal myocyte damage, with or without edema, hemorrhage or vasculitis

**Change Summary**

- Click or tap to enter a date. Choose Action.

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