Medical Policy
Laboratory Tests for Heart and Kidney Transplant Rejection

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Policy Number: 530
BCBSA Reference Number: 2.01.68
NCD/LCD: National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10)

Related Policies
- Heart Transplant, #197
- Heart/Lung Transplant, #269
- ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection, #723

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection is INVESTIGATIONAL.

The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Heartsbreath test is not a covered service.

Medical necessity criteria and coding guidance can be found through the link(s) below.

National Coverage Determinations (NCDs)

National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10)

Note: To review the specific NCD, please remember to click “accept” on the CMS licensing agreement at the bottom of the CMS webpage.

AlloMap test is a covered service.
Medical necessity criteria and coding guidance can be found through the link below.

AlloMap Coding and Billing Guidelines (M00016, V11)

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>Heartsbreath Test is not a covered service. AlloMap Test - Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Heartsbreath Test is not a covered service. AlloMap Test - Prior authorization is not required.</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:**

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
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Description

Heart Transplant Rejection
Noninvasive Heart Transplant Rejection Tests
The Heartsbreath test, a noninvasive test that measures breath markers of oxidative stress, has been developed to assist in the detection of heart transplant rejection. In heart transplant recipients, oxidative stress appears to accompany allograft rejection, which degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes that are, in turn, excreted as volatile organic compounds in breath. The Heartsbreath test analyzes the breath methylated alkane contour, which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes and has been identified as a marker to detect grade 3 (clinically significant) heart transplant rejection.

Another approach has focused on patterns of gene expression of immunomodulatory cells, as detected in the peripheral blood. For example, microarray technology permits the analysis of the expression of thousands of genes, including those with functions known or unknown. Patterns of gene expression can then be correlated with known clinical conditions, permitting a selection of a finite number of genes to compose a custom multigene test panel, which then can be evaluated using polymerase chain reaction techniques. AlloMap is a commercially available molecular expression test that has been developed to
detect acute heart transplant rejection or the development of graft dysfunction. The test involves polymerase chain reaction-expression measurement of a panel of genes derived from peripheral blood cells and applies an algorithm to the results. The proprietary algorithm produces a single score that considers the contribution of each gene in the panel. The score ranges from 0 to 40. The AlloMap website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cutoff for a positive test.1 All AlloMap testing is performed at the CareDx reference laboratory in California.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. They include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most have had low accuracy in diagnosing rejection. Preliminary studies have evaluated the association between heart transplant rejection and micro-RNAs or high-sensitivity cardiac troponin in cross-sectional analyses but the clinical use has not been evaluated.2,3

Renal Transplant Rejection

Donor-Derived Cell-Free DNA Testing
cfDNA, released by damaged cells, is normally present in healthy individuals.4 In patients who have received transplants, dd-cfDNA may be also present. It is proposed that allograft rejection, which is associated with damage to transplanted cells, may result in an increase in dd-cfDNA. AlloSure is a commercially available, next-generation sequencing assay that quantifies the fraction of dd-cfDNA in renal transplant recipients relative to total cfDNA by measuring 266 single nucleotide variants. Separate genotyping of the donor or recipient is not required but patients who receive a kidney transplant from a monozygotic (identical) twin are not eligible for this test. The fraction of dd-cfDNA relative to total cfDNA present in the peripheral blood sample is cited in the report. All AlloSure testing is performed at the CareDx reference laboratory.

Summary
Several commercially available laboratory tests assess heart transplant rejection, including the Heartsbreath test, which measures breath markers of oxidative stress, and the AlloMap test, which uses gene expression profiling. These tests create a score based on the expression of a variety of immunomodulatory genes and are proposed as an alternative or as an adjunct to invasive endomyocardial biopsy. Renal transplant rejection may be assessed by the AlloSure test, which measures the donor-derived cell-free DNA in peripheral blood and is proposed as an alternative or as an adjunct to invasive renal biopsy.

For individuals who have a heart transplant who receive a measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The published study found that, for identifying grade 3 (now grade 2R) rejection, the negative predictive value of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test (78.6%) was better than that for biopsy (42.4%). However, the breath test had a lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than a biopsy (specificity, 97%; positive predictive value, 45.2%). The breath test was also not evaluated for grade 4 rejection. This single study is not sufficient to determine the clinical validity of the test measuring volatile organic compounds and no studies on clinical utility were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a heart transplant who receive gene expression profiling (GEP) to assess cardiac allograft rejection, the evidence includes two diagnostic accuracy studies and several randomized controlled trials evaluating clinical utility. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The 2 studies, Cardiac Allograft Rejection Gene Expression Observation (CARGO, CARGO II) examining the diagnostic performance of GEP for detecting moderate-to-severe rejection lacked a consistent threshold for defining a positive GEP test (ie, 20, 30, or 34) and reported a low number of positive cases. In the available studies, although the negative predictive values were relatively high (ie, at least 88%), the performance characteristics were only calculated based on 10 or fewer cases of rejection; therefore, performance data may be imprecise. Moreover, the positive predictive
value in CARGO II was only 4.0% for patients who were at least two to six months posttransplant and 4.3% for patients more than six months posttransplant. The threshold indicating a positive test that seems to be currently accepted (a score of 34) was not prespecified; rather it evolved partway through the data collection period in the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study. In addition, the IMAGE study had several methodologic limitations (eg, lack of blinding); further, the IMAGE study failed to provide evidence that GEP offers incremental benefit over biopsy performed on the basis of clinical exam or echocardiography. Patients at the highest risk of transplant rejection are patients within one year of the transplant, and, for that subset, there remains insufficient data on which to evaluate the clinical utility of GEP. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a renal transplant and clinical suspicion of allograft rejection who receive testing of donor-derived cell-free DNA to assess renal allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The study examined the diagnostic performance of donor-derived cell-free DNA for detecting moderate-to-severe rejection; the negative predictive value was moderately high (84%), and performance characteristics were calculated on 27 cases of active transplant rejection. The threshold indicating a positive test was not prespecified. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy History**

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<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>1/2019</td>
<td>Investigational policy statement clarified.</td>
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<tr>
<td>7/2018</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>11/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>7/2016</td>
<td>BCBSA National medical policy review. In first policy statement, “grade 3” changed to “grade 2R/grade 3” due to updated ISHLT rejection grades and brand name of test removed; intent of statements unchanged.</td>
</tr>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
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<tr>
<td>10/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
</tr>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines
References


7. Blue Cross Blue Shield Technology Evaluation Center (TEC). Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection. TEC Assessment Program. 2011;26(8).


