Medical Policy

Laboratory Tests for Heart 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/grade 3 heart transplant rejection is INVESTIGATIONAL.

The use of peripheral blood genetic profiling tests in the management of patients after heart transplantation, including but not limited to the detection of acute heart transplant rejection or heart transplant graft dysfunction, is considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

BCBSMA does not cover Heartsbreath test for the following indication for Medicare HMO Blue and Medicare PPO Blue members in accordance with CMS NCD:
- Heartsbreath testing to predict heart transplant rejection improves health outcomes.

National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10)
Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>Outpatient</td>
</tr>
<tr>
<td></td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>Heartsbreath Test is not a covered service.</td>
</tr>
<tr>
<td></td>
<td>AlloMap Test - No</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<td>Heartsbreath Test is not a covered service.</td>
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<tr>
<td></td>
<td>AlloMap Test - No</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:

**CPT Codes**

<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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<tr>
<td>81595</td>
<td>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</td>
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</table>

**Description**

**Heart Transplant Rejection**
Most cardiac transplant recipients experience at least 1 episode of rejection in the first year after transplantation. In 2005, the International Society for Heart and Lung Transplantation modified its grading scheme for categorizing cardiac allograft rejection.1 Revised (R) categories are as follows:

- Grade 0R: No rejection
- Grade 1R: Mild rejection (previously Grades 1A, 1B and 2)
- Grade 2R: Moderate rejection (previously Grade 3A)
- Grade 3R: Severe rejection (previously Grades 3B and 4)

Acute cellular rejection is most likely to occur in the first 6 months, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a life-long basis, dosing is adjusted based on graft function and the grade of acute cellular rejection determined by histopathology. Endomyocardial biopsies are typically taken from the right ventricle via the jugular vein.
periodically during the first 6 to 12 months posttransplant. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following 6 months, and several times (monthly to quarterly) between 6 months and 1 year posttransplant. Surveillance biopsies may also be performed after the first postoperative year (eg, on a quarterly or semiannual basis). This practice, although common, has not been demonstrated to improve transplant outcomes. Some centers no longer routinely perform endomyocardial biopsies after 1 year in patients who are clinically stable.

While endomyocardial biopsy is the criterion standard for assessing heart transplant rejection, it is limited by a high degree of interobserver variability in grading of results and potential morbidity that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy. Finally, biopsy cannot be used to identify patients at risk of rejection, limiting the ability to initiate therapy to interrupt the development of rejection. For these reasons, endomyocardial biopsy is considered a flawed criterion standard by many. Therefore, noninvasive methods of detecting cellular rejection have been explored. It is hoped that noninvasive tests will assist in determining appropriate patient management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false-negative and false-positive biopsy reports. Two techniques have become commercially available for the detection of 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 gene expression of thousands of genes, including those with functions that are 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 (PCR) 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 PCR-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. Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most of these have had low diagnostic 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.

**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 to generate a score based on the expression of various immunomodulatory genes. These tests are proposed as alternatives to, or adjuncts to, endomyocardial biopsy, which is invasive.

For individuals who have heart transplant who are tested with measurement of volatile organic compounds to assess allograft rejection, the evidence includes 1 diagnostic accuracy study. Relevant
outcomes are overall survival, test accuracy and validity, morbid events, and hospitalizations. The published study found that, for identifying grade 3 (grade 2R) rejection, the negative predictive value (NPV) 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 lower specificity (62.4%) and a lower positive predictive value (PPV=5.6%) in assessing grade 3 rejection than biopsy (specificity, 97%; PPV=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 heart transplant who are tested with gene expression profiling (GEP) to assess allograft rejection, the evidence includes 2 diagnostic accuracy studies and several randomized controlled trials (RCTs) evaluating clinical utility. Relevant outcomes are overall survival, test accuracy and validity, morbid events, and hospitalizations. The 2 studies (CARGO, CARGO II) examining the diagnostic performance of GEP for detecting moderate-to-severe rejection lack of a consistent threshold for defining a positive GEP test (ie, 20, 30, or 34) for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (ie, at least 88%), the performance characteristics were calculated based on only 10 or fewer cases of rejection so may be imprecise. Moreover, the PPV in CARGO II was only 4.0% for patients who were at least 2 to 6 months post-transplant and 4.3% for patients more than 6 months post-transplant. The clinical utility of GEP compared with routine endomyocardial biopsies has been evaluated in 2 RCTs, the IMAGE study assessing patients more than 6 months post-transplant and a small pilot RCT assessing patients starting at 55 days post-transplant. 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 IMAGE study. In addition, the IMAGE study had several methodologic limitations (eg, lack of blinding) and it did not determine whether GEP offers incremental benefit over biopsy performed on the basis of clinical exam or echocardiography. Among patients less than 1 year post-transplant, which is the group at highest risk of transplant rejection, there are 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<tbody>
<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. 7/1/2016</td>
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<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. 10/1/2015</td>
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<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


