Laboratory Tests for Heart Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"). unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company considers AlloMap™+ molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the measurement of volatile organic compounds with the Heartsbreath™‡ test to assist in the detection of grade 2R/grade 3 heart transplant rejection to be investigational.*

Background/Overview
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 (GEP) 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.

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. 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
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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 (e.g., 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 gold 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 gold 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 (BMAC), which is derived from the abundance of C4-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. All AlloMap testing is performed at the CareDx reference laboratory in Brisbane, CA.

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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
The U.S. Food and Drug Administration (FDA) has indicated that the Heartsbreath test is only for use as an aid in the diagnosis of grade 3 (now known as grade 2R) heart transplant rejection in patients who have received heart transplants within the preceding year and who have had endomyocardial biopsy within the previous month.

Centers for Medicare and Medicaid Services (CMS)
In December 2008, the Centers for Medicare and Medicaid Services (CMS) issued a noncoverage decision for the Heartsbreath Test. CMS has determined that the evidence does not adequately define the technical characteristics of the test nor demonstrate that Heartsbreath testing to predict heart transplant rejection improves health outcomes in Medicare beneficiaries.

For AlloMap, there is no National Coverage Determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare. In 2012, Palmetto conducted a technical assessment and determined that AlloMap meets Medicare’s reasonable and necessary criteria.

**Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**References**

6. 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).
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Policy History

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12/07/2004  Medical Director review
12/14/2004  Medical Policy Committee review
01/31/2005  Managed Care Advisory Council approval
07/07/2006  Format revision, including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
01/10/2007  Medical Director review
01/17/2007  Medical Policy Committee approval. New policy statement added regarding evaluation of genetic expression in the peripheral blood.
01/07/2009  Medical Director review
01/14/2009  Medical Policy Committee approval. No change to coverage.
01/07/2010  Medical Policy Committee approval
01/20/2010  Medical Policy Committee Implementation approval. No change to coverage.
01/06/2011  Medical Policy Committee approval
03/01/2011  Medical Policy Committee approval
01/19/2011  Medical Policy Committee Implementation approval. No change to coverage.
03/01/2012  Medical Policy Committee review
03/01/2012  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/21/2012  Medical Policy Committee review
05/02/2013  Medical Policy Committee review
05/22/2013  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014  Medical Policy Committee review
05/21/2014  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014  Medical Policy Committee review
11/21/2014  Medical Policy Implementation Committee approval. Added “ Based on review of available data, the Company considers AlloMap molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage.” Used to be considered investigational.
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015  Medical Policy Committee review
11/16/2015  Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016  Medical Policy Committee review
12/21/2016  Medical Policy Implementation Committee approval. Added grade 2R category to policy statement.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
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Next Scheduled Review Date: 12/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>CPT</td>
<td>0085T, 81595, 86849, 93505</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:
  A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
  B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
     1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
     2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
     3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
  A. In accordance with nationally accepted standards of medical practice;
  B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
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C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.