



Louisiana

Laboratory Tests for Heart Transplant Rejection

Policy # 00148

Original Effective Date: 01/31/2005

Current Effective Date: 12/20/2017

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.

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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 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.

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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)

In February 2004, the Heartsbreath test (Menssana Research) was cleared for marketing by the U.S. FDA through a humanitarian device exemption for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The device is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy and is also limited to patients who have had endomyocardial biopsy within the previous month.

In August 2008, AlloMap Molecular Expression Testing (CareDx, Brisbane, CA; formerly XDx) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices, in conjunction with clinical assessment, for aiding in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe transplant rejection. It is intended for patients at least 15 years old who are at least 2 months posttransplant.

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.

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MEASUREMENT OF VOLATILE ORGANIC COMPOUNDS

Approval of the Heartsbreath test by the U.S. FDA was based on the results of the Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) study sponsored by the National Heart, Lung, and Blood Institute. The HARDBALL study was a 3-year, multicenter study of 1061 breath samples in 539 heart transplant patients. Before scheduled endomyocardial biopsy, patient breath was analyzed by gas chromatography and mass spectroscopy for volatile organic compounds. The amount of C4 to C20 alkanes and monomethylalkanes was used to derive the marker for rejection, known as the breath methylated alkane contour. The breath methylated alkane contour results were compared with subsequent biopsy results, as interpreted by 2 readers using the International Society for Heart and Lung Transplantation (ISHLT) biopsy grading system as the criterion standard for rejection.

The authors of the HARDBALL study reported that the abundance of breath markers that measured oxidative stress were found to be significantly greater in grade 0, 1, or 2 rejection than in healthy normal persons. In contrast, in grade 3 rejection, the abundance of breath markers that measure oxidative stress were found to be reduced—most likely due to accelerated catabolism of alkanes and methylalkanes that make up the breath methylated alkane contour. The authors also reported finding that in identifying grade 3 rejection, the negative predictive value (NPV) of the breath test (97.2%) was similar to endomyocardial biopsy (96.7%) and that the breath test could potentially reduce the total number of biopsies performed to assess for rejection in patients at low risk for grade 3 rejection. The sensitivity of the breath test was 78.6% vs 42.4% with biopsy. 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%). In addition, the breath test was not evaluated in grade 4 rejection.

Findings from the HARDBALL study were published in 2004. No subsequent studies evaluating the use of the Heartsbreath test to assess for graft rejection were identified in literature updates.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Laboratory Tests for Heart Transplant Rejection". 2.01.68, 10:2017.
2. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant*. Nov 2005;24(11):1710-1720. PMID 16297770
3. AlloMap: A Non-Invasive, Test Service for Heart Transplant Patients. www.allomap.com. Accessed April, 2016.
4. Duong Van Huyen JP, Tible M, Gay A, et al. MicroRNAs as non-invasive biomarkers of heart transplant rejection. *Eur Heart J*. Dec 1 2014;35(45):3194-3202. PMID 25176944
5. Patel PC, Hill DA, Ayers CR, et al. High-sensitivity cardiac troponin I assay to screen for acute rejection in patients with heart transplant. *Circ Heart Fail*. May 2014;7(3):463-469. PMID 24733367 Phillips M, Boehmer JP, Cataneo RN et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *J Heart Lung Transplant* 2004; 23(6):701-8.
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).
7. Deng MC, Eisen HJ, Mehra MR et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant* 2006; 6(1):150-60.
8. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. *Eur Heart J*. Jan 7 2016. PMID 26746629

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9. Pham MX, Deng MC, Kfoury AG et al. Molecular testing for long-term rejection surveillance in heart transplant recipients: design of the Invasive Monitoring Attenuation Through Gene Expression (IMAGE) trial. J Heart Lung Transplant 2007; 26(8):808-14.
10. Pham MX, Teuteberg JJ, Kfoury AG et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010; 362(20):1890-900.
11. Kobashigawa J, Patel J, Kittleson M, et al. Results of a randomized trial of allomap vs heart biopsy in the first year after heart transplant: Early invasive monitoring attenuation through gene expression profiling trial. J Heart Lung Transplant 2013; 32:s203.
12. Costanzo MR et al, International Society of Heart and Lung Transplantation Guidelines. J Heart Lung Transplant. 2010 Aug;29(8):914-56.
13. Centers for Medicare and Medicaid Services. National Coverage Determination for HEARTSBREATH Test for Heart Transplant Rejection (260.10). 2008; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&CoverageSelection=National&KeyWord=heartsbreath&KeyWordLookUp=Title&KeyWordSearchType=And&clickon=search&bc=gAAAAABAAAAAAA%3d%3d&>. Accessed April, 2016.

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 |
| 01/19/2011 | Medical Policy Committee Implementation approval. No change to coverage. |
| 03/01/2012 | Medical Policy Committee review |
| 03/21/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 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. |

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 12/07/2017 Medical Policy Committee review
 12/20/2017 Medical Policy Implementation Committee approval. No change to coverage.
 Next Scheduled Review Date: 12/2018

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 2016 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:

Code Type	Code
CPT	0085T, 81595, 86849, 93505
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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.

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****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
- 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.

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