



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Breath Test for Detection of Heart Transplantation Rejection**

Effective Date 6/15/2011
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Coverage Policy Number 0456

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Hyperlink to Related Coverage Policies

Genetic Expression Profiles for Detection of Heart Transplantation Rejection (e.g., AlloMap®)
Heart Transplantation
Lung and Heart-Lung Transplantation

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Coverage Policy

CIGNA does not cover breath testing for the detection of heart transplantation rejection (e.g., Heartsbreath test, Menssana Research, Inc., Fort Lee, NJ) because it is considered experimental, investigational or unproven.

General Background

Breath testing (Heartsbreath test, Menssana Research, Inc., Fort Lee, NJ) has been proposed as a non invasive method to measure possible rejection in heart transplant patients. The test is designed to measure oxidative stress in the breath. This is based on the premise that in heart transplant recipients, oxidative stress degrades membrane polyunsaturated fatty acids in membranes by lipid peroxidation, which then releases alkanes and methylalkanes that are in turn excreted as volatile organic compounds in the breath (Williams and Miller, 2002). The Heartsbreath test was developed to analyze the volatile organic compounds, and from this obtain a measure for breath methylated alkane contour, a marker for oxidative stress.

Heart transplantation is the therapy of choice in patients with end-stage heart disease for which there is no other surgical option, and who have received maximal medical treatment and are unlikely to survive the next 6–12 months. One of the serious complications of heart transplantation is organ rejection. Rejection is an immunologic process that, if left unimpeded, results in allograft destruction. The first year after transplantation carries the highest risk of rejection, with the risk of rejection decreasing over time. The diagnosis of rejection may be graded based upon the consensus classification for cardiac allograft rejection published by the

International Society for Heart and Lung Transplantation (ISHLT) (Renlund, et al., 2007; Stewart, et al., 2005). The grades were initially published in 1990 and have been subsequently updated. The current standard cardiac biopsy grading ranges from no rejection to severe rejections (Renlund, et al., 2007; Stewart, et al., 2005).

Endomyocardial biopsy is currently considered the gold standard for detection of tissue rejection in patients who have undergone cardiac transplantation. Biopsies are generally performed weekly for the first six weeks, biweekly until the sixth month, then every one to three months (Phillips, et al., 2004). Most episodes of rejection will usually present with no signs or symptoms and are detected by surveillance biopsies. Endomyocardial biopsies are invasive and may have complications associated with it including: hematoma, infection, arrhythmia, ventricular perforation, and fistulas. There also appears to be a high degree of intraobserver variability in grading the results of the biopsies.

Endomyocardial biopsy has limitations, including the invasiveness of the procedure and potential for complications. This has led to the development of alternatives such as the Heartsbreath test. The value derived from this test has been compared to the results from endomyocardial biopsy. The test was originally developed to be used as an adjunct to, not replacement for, a heart biopsy. According to the Menssana website, the test is also being proposed as a screening test for heart transplant rejection. The developer proposes that if the test is negative, then a biopsy will not be needed and that a biopsy will only be needed if the breath test is positive.

Based on the results from one study evaluating the Heartsbreath test, it appears that this technology is still in the preliminary stages and needs further evaluation and correlation with presence or absence of concurrent disease, such as hemodynamic compromise and infection (Williams and Miller, 2002). There is no evidence that the use of this test will reduce the number of endomyocardial biopsies. While it appears that there may be some clinical utility for use of the breath test in detection of heart transplant rejection in the future, currently the published evidence is not sufficient to allow conclusions regarding the present use of this test in management of heart transplant patients.

U.S. Food and Drug Administration (FDA)

The Heartsbreath test received approval from the U.S. Food and Drug Administration (FDA) under a Humanitarian Device Exemption (HDE) February 2004.

According to the FDA, a humanitarian use device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals in the United States per year. A HUD application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the FDA notes that the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

The HDE allows marketing of the HUD. However, a HUD may only be used after IRB (Institutional Review Board) approval has been obtained for the use of the device for the FDA-approved indication. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated.

The Heartsbreath test was approved as an HUD 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 Heartsbreath test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy within the previous month.

Literature Review

Phillips et al. (2004) conducted a study to evaluate a marker of heart transplant rejection, the breath methylated alkane contour, referred to as the HARDBALL study. The study involved 539 heart transplant recipients studied at seven sites. Breath samples (n=1061) were collected on the day of scheduled endomyocardial biopsy, before the biopsy was performed. The breath test measured the breath methylated alkane contour, and these results were compared to results of the biopsies. The biopsies were evaluated and graded by two reviewers in addition

to the pathologist at each site. The biopsies were graded using the IS HLT rejection grades. The independent reviewer's biopsy results indicated: 645 patients (60.8%) with ISHLT rejection grade 0; 281 (26.5%) with rejection grade 1; 93 (8.8%) with rejection grade 2; and 42 (4.0%) with rejection grade 3. Compared with the independent reviewers, the site pathologist had a sensitivity of 42.4% and specificity of 97.0% for grade 3 rejection. The breath tests revealed nine volatile organic compounds that represented markers of grade 3 rejection. In a predictive model, the breath markers had sensitivity of 78.6% and specificity of 62.4%. The negative predictive value of the breath test for grade 3 rejections was 97.3%.

Professional Societies/Organizations

Professional society guidelines addressing the use of breath test for detection of heart transplant rejection are lacking.

Summary

There is insufficient evidence in the published, peer-reviewed scientific literature to conclude that the breath test for detection of heart transplant rejection results in improved management of heart transplant recipients. Likewise, there is insufficient evidence that use of this test will result in earlier or more efficient detection of heart transplant rejection or that this test is equal to or superior than the standard test, endomyocardial biopsy. Well-designed clinical trials are needed to further evaluate the potential utility of this test and define the role of the test in management of heart transplantation.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT ^{®*} Codes	Description
0085T	Breath test for heart transplant rejection

ICD-9-CM Diagnosis Codes	Description
V42.1	Heart replaced by transplant
	All other codes

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

References

1. American Heart Association (AHA). Heart Transplants: Statistics. Accessed April 19, 2011. Available at URL address: <http://www.americanheart.org/presenter.jhtml?identifier=4588>
2. Bonow RO, Mann DL, Zipes DP, Libby P editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 9th edition. Philadelphia: Elsevier Inc.; 2011.
3. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for HEARTsbreath Test for HEART TRANSPLANT Rejection (260.10). 12/8/2008. Accessed April 19, 2011. Available at URL address: <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=325&ncdver=1&bc=BAABAAAAAAAA&>
4. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al.; International Society of Heart and Lung Transplantation Guidelines. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010 Aug;29(8):914-56.

5. International Society of Heart and Lung Transplantation. Guidelines for the care of heart transplant recipients. Task force 2: immunosuppression and rejection. Nov 2010. Accessed April 27, 2011. Available at URL address: <http://www.isHLT.org/publications/guidelines.asp>
6. Kaplan AV, Harvey ED, Kuntz RE, Shiran H, Robb JF, Fitzgerald P. Humanitarian Use Devices/Humanitarian Device Exemptions in cardiovascular medicine. *Circulation*. 2005 Nov 1;112(18):2883-6.
7. Patel JK, Kobashigawa JA. Should we be doing routine biopsy after heart transplantation in a new era of anti-rejection? *Curr Opin Cardiol*. 2006 Mar;21(2):127-31.
8. Phillips M, Boehmer JP, Cataneo RN, Cheema T, Eisen HJ, Fallon JT, et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *J Heart Lung Transplant*. 2004 Jun;23(6):701-8.
9. Phillips M, Boehmer JP, Cataneo RN, Cheema T, Eisen HJ, Fallon JT, et al. Prediction of heart transplant rejection with a breath test for markers of oxidative stress. *Am J Cardiol*. 2004 Dec 15;94(12):1593-4.
10. Renlund DG, Taylor DO, Smedira NG. Cardiac transplantation and mechanical circulatory support. Cardiac allograft rejection. In: Topol EJ, editor. *Textbook of Cardiovascular Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2007. p 1429-36.
11. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant*. 2005 Nov;24(11):1710-20.
12. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Humanitarian Use Devices. Accessed April 19, 2011. Available at URL address: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm>
13. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). New Humanitarian Device Approval. Heartsbreath test. February 24, 2004. Accessed April 19, 2011. Available at URL address: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081213.htm>
14. Williams ES, Miller JM. Results from late-breaking clinical trial sessions at the American College of Cardiology 51st Annual Scientific Session. *J Am Coll Cardiol*. 2002 Jul 3;40(1):1-18.

Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	6/15/2008	0456	Breath Test for Detection of Heart Transplantation Rejection

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