

Corporate Medical Policy

Laboratory Tests for Heart Transplant Rejection

File Name: laboratory_tests_for_heart_transplant_rejection
Origination: 7/2005
Last CAP Review: 4/2012
Next CAP Review: 4/2013
Last Review: 4/2012

Description of Procedure or Service

The majority of cardiac transplant recipients experience at least one episode of rejection in the first year after transplantation. 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 on a weekly basis for the first month, and once or twice monthly for the following 6 months. Surveillance biopsies may also be performed on a yearly basis following stabilization. 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 a year post-transplant. Surveillance biopsies may also be performed after the first postoperative year e.g., on a quarterly or semi-annual basis. This practice, although common, has not been demonstrated to improve transplant outcomes. Due to the low rate of rejection after a year, some centers no longer routinely perform endomyocardial biopsies after a 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 non-invasive 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.

The Heartsbreath test (Menssana Research, Inc.) is a noninvasive test that measures breath markers of oxidative stress that has been developed to assist in the detection of heart transplant rejection. In heart transplant recipients, oxidative stress appears to accompany allograft rejection that 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 (significant) heart transplant rejection.

The Heartsbreath test received approval from the U.S. Food and Drug Administration (FDA) through a humanitarian device exemption in February 2004. The Heartsbreath test is indicated 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

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not as a substitute for, endomyocardial biopsy, and is also limited to patients who have had endomyocardial biopsy within the previous month.

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. All AlloMap testing is performed at the XDx reference laboratory in Brisbane, CA. The test involves PCR expression measurement of a panel of genes derived from peripheral blood cells, and applies an algorithm to the results. The algorithm produces a single score that considers the contribution of each gene in the panel. The score ranges from 0 to 40. The XDx website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cut-off for a positive test.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Breath testing for heart transplant rejection detection is considered investigational. BCBSNC does not provide coverage for investigational services.

Evaluation of genetic expression in the peripheral blood to detect acute heart transplant rejection or graft dysfunction is considered investigational. BCBSNC does not provide coverage for investigational services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Laboratory Tests for Heart Transplant Rejection is covered

Not Applicable

When Laboratory Tests for Heart Transplant Rejection is not covered

The measurement of volatile organic compounds in breath to assist in the detection of grade 3 heart transplant rejection is considered investigational.

The evaluation of genetic expression in the peripheral blood, including, but not limited to, the detection of acute heart transplant rejection or graft dysfunction is considered investigational.

Policy Guidelines

Although studies show promising results, current data are inadequate to permit scientific conclusions regarding the use of the Heartbreath test in the management of heart transplant recipient. No published studies or abstracts were found that examined how either test could be integrated into the management of the patient, either to select or deselect patients for

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endomyocardial biopsy, or potentially replace endomyocardial biopsy altogether.

The FDA has indicated that the Heartsbreath test is only 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 and who have had endomyocardial biopsy within the previous month.

A BCBSA TEC Assessment was published in 2011. The assessment concluded that additional clinical experience is needed regarding the AlloMap™ test to confirm and extend the current results, and to address several important questions such as the best cutoff value and when to test. Furthermore, the impact of this test on management decisions and health outcomes is unknown. Frequent monitoring with AlloMap™ could potentially result in an increase in the number of biopsies performed in stable patients who would not otherwise undergo routine biopsy. Evidence to date is insufficient to permit conclusions concerning the effect of the technology on health outcomes. Therefore, routine use of gene expression profiling in post-transplantation surveillance is considered investigational.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0085T, 86849

There are no specific codes for the AlloMap™ test.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy titled: Breath Testing for Heart Transplant Rejection Detection

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.68, 11/9/2004.

Specialty Matched Consultant Advisory Panel - 11/05

Phillips M, Cataneo RN, Greenberg J, Gunawardena R, Naidu A, Fahbari-Oskoui F. Effect of age on the breath methylated alkane contour, a display of apparent new markers of oxidative stress. *J Lab Clin Med* 2000;135:243-9.

Phillips M, Boehmer JP, Cataneo RN, Cheema T, Eisen JG, Fallon JT. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *J Heart Lung Transplant*. 2004 Jun;23(6):701-8.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.68, 12/12/06.

U.S. Food and Drug Administration (FDA). Humanitarian Device Exemption H030004. Summary of Safety and Probably Benefit. Retrieved 8/3/07 from <http://www.fda.gov/cdrh/pdf3/H030004b.pdf>

For Policy renamed: Laboratory Tests for Heart Transplant Rejection

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California Technology Assessment Forum (CTAF). Gene expression profiling for the diagnosis of heart transplant rejection. San Francisco, CA: 2006. Retrieved from <http://www.ctaf.org/content/general/detail/624>.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.68, 11/13/08

Centers for Medicare and Medicaid Services. National Coverage Determination. Heartsbreath Test for Heart Transplant Rejection (CAG-00894N), December 8, 2008. Retrieved 7/30/09 from <https://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=217&>

Tice JA. Gene expression profiling for the diagnosis of heart transplant rejection. California Technology Assessment Forum. October 13, 2010.

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. N Engl J Med 2010; 362(20).

Jarcho JA. Fear of rejection- monitoring the heart-transplant recipient. N Engl J Med 2010; 362(20): 1932-3.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.68, 11/11/10

Senior Medical Director review 2/2011

Specialty Matched Consultant Advisory Panel review 4/2011

Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection. TEC Assessments 2011.

Specialty Matched Consultant Advisory Panel review 4/2012

Policy Implementation/Update Information

For Policy titled: Breath Testing for Heart Transplant Rejection Detection

- 7/7/2005 New policy issued. Breath testing for heart transplant rejection detection is considered investigational. Notification given 7/7/2005. Policy effective 9/15/2005.
- 11/17/05 Specialty Matched Consultant Advisory Panel review 11/07/05. No change to policy.
- 11/19/07 References updated. Specialty Matched Consultant Advisory Panel review meeting
- 10/29/07. No change to policy statement. (adn)

For Policy renamed: Laboratory Tests for Heart Transplant Rejection

- 12/7/09 Policy name changed from "Breath Testing for Heart Transplant Rejection Detection" to "Laboratory Tests for Heart Transplant Rejection." Description section revised for clarity. Added the following Policy Statement: BCBSNC does not provide coverage for the evaluation of genetic expression in the peripheral blood to detect acute heart transplant rejection or graft dysfunction. It is considered investigational. Statement in the Not Covered section revised to read: The measurement of volatile organic compounds in breath to assist in the detection of grade 3 heart transplant rejection is

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considered investigational. Also added the following statement to the Not Covered section: The evaluation of genetic expression in the peripheral blood, including, but not limited to, the detection of acute heart transplant rejection or graft dysfunction is considered investigational. Policy Guidelines updated to include FDA information regarding the Heartsbreath test and rationale for the investigational status of the AlloMap™ test. References updated. Specialty Matched Consultant Advisory Panel review meeting 10/30/09. Approved policy revisions. (adn)

- 6/22/10 Policy Number(s) removed (amw)
- 10/26/10 CPT code 86849 added to Billing/Coding section. (mco)
- 3/1/11 Description section updated. References updated. Reviewed by Senior Medical Director. (mco)
- 5/10/11 Specialty Matched Consultant Advisory Panel review 4/2011. References updated. (mco)
- 5/15/12 Specialty Matched Consultant Advisory Panel review 4/2012. Description section updated. Policy Guidelines updated. References updated. (mco)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.