



**Kaiser Foundation Health Plan  
of Washington**

**Clinical Review Criteria**

**Laboratory Tests for Detection of Heart Transplantation Rejection**

- AlloMap® Heart (Molecular Expression Testing, CareDx)
- Heartsbreath Test

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**Criteria**

**For Medicare Members**

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	<a href="#">Heartsbreath Test for Heart Transplant Rejection (260.10)</a> <i>*The Heartsbreath test is not covered per Medicare criteria.</i>
Local Coverage Determinations (LCD)	<a href="#">MoIDX: Molecular Diagnostic Tests (MDT) (L36256)</a>
Local Coverage Article	<a href="#">AlloMap Billing and Coding Guidelines (A54366)</a>

**For Non-Medicare Members**

Service	Criteria
AlloMap Test	AlloMap is covered for patients who have undergone heart transplant.  <b>If requesting this service, please send the following documentation to support medical necessity:</b> <ul style="list-style-type: none"> <li>• Last 6 months of clinical notes from requesting provider &amp;/or specialist</li> <li>• Last 6 months of radiology notes if applicable</li> </ul>
Heartsbreath Test	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.  <b>If requesting review for this service, please send the following documentation:</b> <ul style="list-style-type: none"> <li>• Last 6 months of clinical notes from requesting provider &amp;/or specialist</li> </ul>

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

## Background

Approximately 3,500 people worldwide now undergo heart transplantation every year with at least 40% of recipients experiencing at least one episode of rejection in the first year after transplantation (Stehlik, Edwards et al. 2012). Clinical features of acute cellular rejection are unreliable resulting in a variety of monitoring techniques which may include frequent blood tests, lung function tests, electrocardiograms echocardiograms and biopsies of the heart tissue.

The current gold standard for heart transplant rejection diagnosis is a series of endomyocardial biopsies (EMB) (Miller, Fildes et al. 2013). Typically, EMB is performed through the jugular or femoral veins and is invasive, painful and commonly associated with risks of procedural complications (From, Maleszewski et al. 2011). With rejection most likely to occur within the first year after transplant, EMB is performed and repeated frequently post-transplant exposing patients to long-term complications including, but not limited to, severe tricuspid valve regurgitation. Additional limitations include, evidence indicating discrepancies in biopsy readings by different pathologists sufficient to demonstrate adverse treatment implications (Winters and McManus 1996) and finally, the notion that 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, the gold standard has been considered flawed resulting in many attempts to develop non-invasive tools to detect heart transplant rejection.

Gene expression profiling (GEP) of circulating leukocytes has been recently introduced as a new non-invasive modality for cardiac allograft rejection monitoring. This is based on the assumption that recirculating peripheral blood mononuclear cells (PBMC) may reflect earlier host responses to the allograft than those at local sites. The test uses real-time polymerase chain reaction (PCR) technology to measure the expression of 20 genes (11 informative, 9 control and normalization). Using a multigenic algorithm, a score ranging from 0 to 40 is generated. Some researchers found that this score may discriminate between quiescence and moderate/severe acute rejection. The lower scores are associated with a very low likelihood of moderate/severe graft rejection (Starling 2006). The score however, may be influenced by several factors including time post-transplant, peripheral alloimmune activity, corticosteroid dose, and cytomegalovirus infection (Yamani 2007, Starling 2006). According to Starling and colleagues (2006), the candidates for GEP testing are clinically stable cardiac transplant recipients, >15 years of age, > 6 months post-transplant, and at low risk for moderate/severe cellular rejection. It was also reported that the frequency of performing a GEP test to monitor the rejection should be individualized according to the patient's rejection history, immunosuppression regimen, time post transplant, and transplant centre protocol. The GEP test is not recommended for patients at high risk for acute rejection or graft failure, <15 years of age, pregnant women, patients who had a blood transfusion within 12 months before the transplant, received hematopoietic growth factors within the previous 30 days, high dose steroids within the past 21 days, or are on >20 mg/day of prednisone equivalent.

AlloMap® gene expression test, XDx, Inc, South San Francisco, CA, is the first commercially available molecular test developed for acute rejection monitoring. The test was introduced for clinical use in January 2005. It uses simple blood samples and is performed at CLIA-certified XDx laboratory in South San Francisco.

Currently, potential non-invasive alternatives to biopsy range from imaging techniques to genetic expression profiling with limited established evidence (Miller, Fildes et al. 2013). The Heartsbreath test™ (HBT) was developed by Menssana Research, Inc. and is an intrinsically safe, painless and non-invasive test for heart transplant rejection. The HBT is currently indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the previous year (Menssana 2004). It is meant for use in addition to, and not as a substitute for, EMB. The HBT works specifically by measuring the amount of methylated alkanes in a patient's breath with the rationale based on two observations the first being that allograft rejection is accompanied by oxidative stress resulting from increased production of reactive oxygen species in the myocardium (Schimke, Schikora et al. 2000) and, the second, that reactive oxygen species degrade cellular membranes by lipid peroxidation of polyunsaturated fatty acids generating alkanes that are excreted in the breath as volatile organic compounds and may provide markers of the intensity of rejection (Kneepkens, Ferreira et al. 1992). The HBT subtracts the amount of methylated alkanes in a patient's breath from the number of methylated alkanes in the room's air (Phillips 1997). The value generated by the test is compared to the results of a biopsy performed during the previous month to measure the probability of the implanted heart being rejected. The test's greatest value may be in helping to separate less severe organ rejection (grade 0,1 and 2) from more severe organ rejections (grade 3). In general, the evaluation of non-invasive techniques for the identification of heart transplant rejection is difficult due to the imperfect nature of the current gold standard.

The FDA approved the HBT under the Humanitarian Device Exemption program in February of 2004 to be used in patients who have had heart transplants within the past year (FDA 2004). A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year (FDA 2010). A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in treatment or diagnosis of diseases affecting these populations. The labeling for a 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.

## Medical Technology Assessment Committee (MTAC)

### *AlloMap in the Detection of Cardiac Allograft Rejection*

#### 06/04/2007: MTAC REVIEW

**Evidence Conclusion:** The CARGO study was an observational study conducted to develop and evaluate a gene expression profiling test (AlloMap test) from peripheral blood mononuclear cells sample to discriminate between quiescence (grade 0 rejection) and moderate /severe (grade >3A) rejection in heart transplant patients, according to the International society for Heart Lung Transplantation (ISHLT) grading. The endomyocardial biopsy (EMB) was used as the gold standard for detecting acute cellular rejection. EMB however has its limitation. It may only detect rejection after cellular infiltration and/or graft damage has occurred and cannot be repeated beyond a certain frequency. In addition, its histopathological interpretation and grading is often not clear-cut, and subject to sampling error and inter observer variability. Overall the results of the study showed that at a predefined threshold of 20 (score range 0-40), the test had an 84% sensitivity to detect a grade >3A rejection compared to the endomyocardial biopsy. After one-year post-transplant the test had a very high negative predictive value (99.6%) i.e. very high ability to rule out moderate /severe rejection. It however had a very low positive predictive value (6.8%) and low specificity (approximately 40%). The study evaluated the ability of the test to discriminate between quiescence and moderate/severe rejection of the transplant. There is no published evidence to date on the clinical outcomes associated with using the test for long-term monitoring of cardiac rejection, on the predictive capacity of the test for future clinical events, or its effect on improving the management of the patients, e.g. tailoring and individualizing immunosuppressive medications. The "Invasive Monitoring Attenuation through Gene Expression" (IMAGE) ongoing study might provide evidence on the long-term health outcomes associated with this gene expression testing.

**Articles:** The literature search yielded just over 20 articles, the majority of which were reviews and editorials. There was a relatively large observational study (CARGO) that evaluated the ability of gene expressing profiling of peripheral blood test to discriminate between quiescence and from moderate/severe rejection in cardiac allograft recipients, two small case series, and a few other observational studies published in abstract forms. The CARGO study was selected for critical appraisal. Deng MC, Eisen HJ, Mehra MR, et al for the Cardiac allograft Rejection Gene Expression Observational (CARGO) study Investigators. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant.*2006;6:150-160. See [Evidence Table](#).

The use of AlloMap in the detection of cardiac allograft rejection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

#### 08/19/2003: MTAC REVIEW

### *Heartsbreath Test in the Detection of Cardiac Allograft Rejection*

**Evidence Conclusion:** The HARDBALL (heart allograft rejection: detection with breath alkanes in low levels) study was a three-year multicenter case-control study supported by the National Heart Lung and Blood Institute (Philips, Boehmer et al. 2004). The original clinical study evaluated a new marker of heart transplant rejection, the breath methylated alkane contour (BMAC) with the idea that rejection is accompanied by oxidative stress which degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes which are excreted in the brain as volatile organic compounds (VOCs). Prior to scheduled EMB, the HBT was employed on 539 heart transplant recipients to collect 1061 breath VOC samples. The breath VOCs were analyzed by gas chromatography and mass spectroscopy, and the BMAC was derived from the abundance of C4-C20 alkanes and monomethylalkanes. The gold standard of rejection was the concordant set of International Society for Heart and Lung Transplantation (ISHLT) grades in biopsies read by two cardiac pathologists. The authors of the HARDBALL study reported that the abundance of breath markers of oxidative stress was significantly greater in grade 0,1 or 2 rejection than in healthy normal persons. Whereas in grade 3 rejection, the abundance of breath markers of oxidative stress was reduced most likely due to accelerated catabolism of alkanes and methyl alkanes that comprise the BMAC. The authors also reported finding that in identifying grade 3 rejection, the negative

predictive value of the breath test (97.2%) was similar to EMB (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 (5.6%) in assessing grade 3 rejection than biopsy (specificity 97%, positive predictive value 45.2%). Additionally, the breath test was not evaluated in grade 4 rejection. Breath test results revealed nine breath samples whose levels represented markers of grade 3 rejection. The cross-validated model, indicated that the HBT had a sensitivity of 59.5% and specificity of 58.8% for detecting grade 3 heart transplant rejection, compared to biopsy. The negative predictive value of the breath test for grade 3 rejection was 97.3% such that in a patient with a negative breath test, EMB would contribute little additional clinical information.

Limitations include a surprising lack of consistency between biopsy interpretation by the pathologists at the transplant program site and the independent pathologist working with the authors. The study results are made difficult to interpret given these disparities. Further studies should investigate the HBT in populations with concurrent patient illness which theoretically, could affect the markers of oxidative stress. It is also important to note that the primary investigator has substantial financial and professional ties with the developer of the device under investigation. The major potential benefit of the HBT would be that it may reduce the risk of a patient getting the wrong treatment because of an erroneous biopsy report. Despite the clear potential benefits that a non-invasive approach such as the HBT could offer, there is no evidence to demonstrate that the use of the HBT will result in better patient management and improvements in health outcomes. Ultimately, a clinically meaningful investigation of the HBT would require assessment in multicenter, outcome-based trials with adequate power, blinding and randomization to control for baseline differences between groups and determine whether additional testing provides a significant advantage over the standard of care in any of the proposed uses of these laboratory tests.

**Articles:** A search of the PubMed database as well as the Clinical Trials database was completed for the period from database inception through June 2013 for studies on the diagnostic value of the Heartsbreath Test for patients with heart allograft rejection. The search strategy used the terms non-invasive, heart transplant, rejection, Heartsbreath and test with variations. Articles were limited to those published in English language and with enrolled human subjects. The search was supplemented by an examination of article bibliographies in addition to the PubMed related articles function. The HARDBALL study was selected for critical appraisal:

Phillips M, Boehmer JP, Cataneo RN, et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *The Journal of Heart and Lung Transplant* 2004;23(6):701-708. [See Evidence Table](#)

The use of Heartsbreath test in the detection of cardiac allograft rejection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

## Applicable Codes

**AlloMap - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

CPT® Codes	Description
81595	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

**Heartsbreath - Considered Not Medically Necessary:**

CPT® Codes	Description
No specific codes	

**\*Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

\*\*To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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Date Created	Date Reviewed	Date Last Revised
06/26/2007	09/06/2011 <sup>MDCRPC</sup> , 07/03/2012 <sup>MDCRPC</sup> , 04/02/2013 <sup>MDCRPC</sup> , 05/07/2013 <sup>MDCRPC</sup> , 10/01/2013 <sup>MPC</sup> , 03/04/2014 <sup>MPC</sup> , 01/06/2015 <sup>MPC</sup> , 11/03/2015 <sup>MPC</sup> , 09/06/2016 <sup>MPC</sup> , 07/11/2017 <sup>MPC</sup> , 05/01/2018 <sup>MPC</sup> , 05/07/2019 <sup>MPC</sup> , 05/05/2020 <sup>MPC</sup> , 05/04/2021 <sup>MPC</sup> , 05/03/2022 <sup>MPC</sup> , 05/02/2023 <sup>MPC</sup>	05/04/2021

<sup>MDCRPC</sup> Medical Director Clinical Review and Policy Committee

<sup>MPC</sup> Medical Policy Committee

Revision History	Description
07/28/2016	Added LCA for AlloMap
12/20/2018	AlloMap is now covered for member who have had a heart transplant (before they had to fail biopsy)
05/04/2021	Removed deleted code 0085T for Heartsbreath