Medical Policy

Subject:	Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection		
Document #:	TRANS.00025	**Publish Date:**	04/07/2021
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Description/Scope

This document addresses specific noninvasive laboratory tests for the early detection of rejection following a heart transplant. This includes the Heartsbreath test (Menssana Research, Inc. Fort Lee, NJ), which measures the chemical byproducts of allograft rejection and has been investigated to potentially make the process of monitoring heart transplant recipients safer and less complicated. Also addressed in this document is the AlloMap® molecular expression testing (CareDx®, Inc., Brisbane, CA) which has also been investigated as a noninvasive method of determining the risk of rejection in heart transplant recipients.

Even with modern drug therapy, rejection remains a constant hazard, and transplant recipients must be tested repeatedly for signs of renewed rejection. Currently, the gold standard to detect heart transplant rejection is endomyocardial biopsy. This is typically performed weekly for the first 6 weeks, biweekly until the third month, monthly to 6 months and then every 1 to 3 months, as indicated.

Position Statement

Medically Necessary:

AlloMap molecular expression testing is considered **medically necessary** as a non-invasive method of determining the risk of rejection in heart transplant recipients between 1 and 5 years post-transplant.

Investigational and Not Medically Necessary:

Breath testing with the Heartsbreath test is considered **investigational and not medically necessary** for use as an aid in the diagnosis of heart transplant rejection.

AlloMap molecular expression testing is considered **investigational and not medically necessary** when the criteria above are not met.

Rationale

Breath Test

Heartsbreath (Breath test for Grade 3 heart transplant rejection), manufactured by Menssana Research, Inc., (Fort Lee, NJ) received U.S. Food and Drug Administration (FDA) clearance on February 24, 2004 under the Humanitarian Device Exemption (HDE)* program with the following indications for use:

> 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 Heartsbreath test is intended for use 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 (EMB) within the previous month (FDA, 2004).

The Heartsbreath test works on the principle that rejection of the transplanted heart is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes that are excreted in the breath as volatile organic compounds (VOCs). The individual breathes for 2 minutes through a disposable mouthpiece attached to a breath collecting device, which then analyzes the VOCs in alveolar and room air and interprets the values, using a proprietary algorithm to predict the probability of Grade 3 heart transplant (HT) rejection.

The Heartsbreath test should not be used for individuals who have received an HT more than 1 year ago, or have a Grade 4 HT rejection, because Heartsbreath has not been evaluated in these groups.

FDA clearance was based on the results of the Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) Study, which was sponsored by the National Heart Lung and Blood Institute (NHLBI). In this 3-year multicenter study, investigators evaluated a new marker of HT rejection, the breath methylated alkane contour (BMAC). In the HARDBALL study, 1061 breath VOC samples were collected from 539 HT recipients at seven sites on the day of scheduled EMB. 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. Results included concordant biopsies of:

- Grade 0, 645 of 1061 (60.8%);
- Grade 1A, 197 (18.6%);
- Grade 1B, 84 (7.9%);
- Grade 2, 93 (8.8%);
- Grade 3A, 42 (4.0%).

A combination of 9 VOCs in the BMAC identified Grade 3 rejection (sensitivity 78.6%; specificity 62.4%; cross-validated sensitivity 59.5%; cross-validated specificity 58.8%; positive predictive value [PPV] 5.6%; negative predictive value [NPV] 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, PPV 45.2% and NPV 96.7%. The authors concluded that a breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 HT rejection than a biopsy reading by a single on-site pathologist, but the NPV of the two tests were similar. They concluded that a negative screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and obviate the need for EMB in this group, thereby reducing the overall number of EMBs performed, which was estimated to be by as much as 50% (Phillips, 2004).

Currently, there is inadequate evidence in the published literature to demonstrate the safety, efficacy, and clinical utility of the Heartsbreath test in the management of rejection surveillance following HT. Large trials are needed to further define the role of this technology and demonstrate how use of this test will impact treatment management.

AlloMap Molecular Expression Testing

The AlloMap molecular expression blood test was developed by XDx, Inc. (South San Francisco, CA), now known as CareDx, Inc., (Brisbane, CA). In 2008, FDA 510(k) clearance as a Class II approval was granted for AlloMap Molecular Expression Testing as an in-vitro, diagnostic, multivariate, index assay test service, which assesses the gene expression profile of RNA isolated from peripheral blood mononuclear cells for the following indication:

> To aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment. AlloMap is indicated for use in heart transplant recipients who are 15 years of age or older and at least 2 months (greater than or equal to 55 days) post-transplantation (FDA, 2008).

The test assesses the expression of 20 genes, about half of which are directly involved in rejection while the remainder provide other information needed for rejection risk assessment. It is hoped the results of this test will decrease the number of necessary EMBs. Among the proposed benefits are the AlloMap test's ability to differentiate mild rejection, for which histologic findings may be the least accurate, and the potential for monitoring physiologic responses to steroid weaning. It has been recognized that the test is not effective at monitoring rejection within the first 6 months of transplantation, and it is yet unclear what a high AlloMap score might mean in the setting of no histologic rejection.

These patterns of gene expression, detected in peripheral blood by the AlloMap testing, were studied in the Cardiac Allograft Rejection Gene Expression Observation Study (CARGO), which included eight U.S. cardiac transplant centers where 650 HT recipients were tested. Results of the CARGO study have appeared in abstracts presented at the 2005 annual meeting of the ISHLT. While the results were promising, the data was considered inadequate to permit firm scientific conclusions regarding how use of this test will impact the management of HT recipients (Deng, 2006). There have been subsequent validation studies and sub-study analyses of the CARGO results which provided additional data regarding the potential utility of the AlloMap test in detecting transplant rejection (Bernstein, 2007; Mehra, 2007b; Mehra, 2008). More recent results of the CARGO and the CARGO II trial, a European based observational study to further validate the gene expression profiling (GEP) test performance of AlloMap, have been published with findings that reflect similar results. For greater than or equal to 2-6 months and greater than 6 months post-transplantation, the CARGO II GEP score performance (AUC-ROC=0.70 and 0.69) is similar to the CARGO study results (AUC-ROC=0.71 and 0.67). It was the opinion of the trial investigators that the low prevalence of ACR contributed to the high NPV and limited PPV of GEP testing. The authors concluded that choice of threshold score for the practical use of GEP testing with AlloMap should consider the overall clinical assessment of the individual's baseline risk for rejection (Crespo-Leiro, 2015; 2016).

Results of another trial were published in 2010. The Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial, which was sponsored by the manufacturer of AlloMap (XDx, Inc.), was a randomized, event-driven, noninferiority trial which was conducted at 13 U.S. transplant centers between January 2005 and October 2009 (with median follow-up of 19 months). This trial included 602 selected transplant recipients who had undergone a transplant more than 6 months prior and who were considered at low risk for rejection. The purpose of this study was to compare rejection outcomes between those who underwent routine EMB and those who were monitored with the AlloMap GEP test. The primary outcome was the first occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. Results indicated that a strategy of monitoring for rejection that involved GEP, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies. During the median follow-up period (19 months), subjects who were monitored with AlloMap and those who underwent routine EMB had similar 2-year cumulative rates of the composite primary outcome (14.5% and 15.3%, respectively; hazard ratio [HR] with GEP, 1.04; 95% confidence interval [CI], 0.67 to 1.68). The 2-year rates of death from any cause were also similar in the two groups (6.3% and 5.5%, respectively; p=0.82). Although the limited power of the study did not allow for firm conclusions regarding the utility of AlloMap as a substitute for

EMB, the authors concluded that GEP of peripheral blood specimens may offer a reasonable alternative to routine EMB, for monitoring cardiac transplant rejection, if the interval since transplantation is at least 6 months and the individual is considered to be at low risk for rejection (Pham, 2010).

In 2010, the ISHLT issued guidelines for the care of HT recipients which included the following:

- The standard of care for adult HT recipients is to perform periodic EMB during the first 6-12 months after transplant for rejection surveillance; (Class IIa, Level of Evidence: C)
- After the first year post-transplant, EMB surveillance every 4-6 months is recommended for patients at higher risk of late acute rejection; (Class IIa, Level of Evidence: C)
- GEP using the AlloMap test can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients between 6 months and 5 years post-transplant (Class IIa, Level of Evidence: B) (Costanzo ISHLT, 2010).

Another 2010 portion of the ISHLT guideline titled, "Task Force 2: Immunosuppression and Rejection" noted the following regarding the grading scale for risk of ACR in HT recipients:

> Due to intra- and interobserver variability in the determination of the different grades of mild or moderate rejection and the observation that grades 1 and 2 were mostly self-limited, a revised heart allograft rejection grading system was published in 2005 as follows (Stewart, 2005):
>
> - Grade 0 (no cellular rejection) was now named grade 0R ('R' added to reflect the revised 2005 scale);
> - The intermediate grades of 1A, 1B, and 2 were re-classified as grade 1R, or mild ACR;
> - Grades 3A was re-classified as grade 2R, moderate ACR; and
> - Grade 3B and 4 were re-classified as grade 3R, severe ACR.
> - In addition, AMR (antibody mediated rejection) was recognized as a clinical entity, and recommendation was issued for determination of its presence (AMR1) or absence (AMR0) (Taylor ISHLT, 2010).

The recommendation for AlloMap is based on the results of the CARGO and IMAGE trials (Costanzo, 2010).

In summary, the current ISHLT recommendations for the use of AlloMap in limited clinical protocols are the results of the IMAGE trial, and input from the transplant practice community supports the use of AlloMap to assess risk for ACR in clinically stable HT recipients between 1 and 5 years post-transplant.

Background/Overview

Breath Test

Although the current gold standard test for detecting rejection is EMB, this is limited in accuracy, has a high degree of inter-observer variability, and may yield tissue that is not representative of the overall pathology. It is also invasive and can lead to infections, arrhythmias, or ventricular perforation. Despite these limitations, the breath test is currently not established as a substitute for EMB.

***Note:** A Humanitarian Use Device (HUD) is a device that has been given special approval by the FDA under the Humanitarian Device Exemption (HDE) regulations and is utilized in special circumstances where a condition is so rare (fewer than 4000 individuals in the U.S. per year) that testing of large numbers of subjects is not feasible. In these special situations, the FDA may grant an HDE provided that: the device does not pose an unreasonable or significant risk of illness or injury; and 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 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. (FDA, 2004)

AlloMap Molecular Expression Testing

The California Technology Assessment Forum (CTAF) conducted a technology assessment of GEP for the diagnosis of HT rejection in 2006, at which time it was determined that the use of GEP did not meet CTAF criteria when used to manage HT patients. The CTAF assessment stated that:

> Gene expression profiling offers the potential for a non-invasive test that may replace endomyocardial biopsy as the gold standard for transplant rejection. However, given the history of poor reproducibility of other gene expression profiles in the recent past, it is prudent to require independent confirmation of the CARGO study results before widespread adoption of the AlloMap gene expression profile to monitor heart transplant patients for early detection of rejection (CTAF, 2006).

This initial CTAF determination was based on concerns around the post-hoc change in the threshold used to define a positive test result in the CARGO study and the small size of this primary validation study, in addition to the fact that there were no studies, published to date, comparing the clinical outcomes of individuals monitored with GEP to those monitored with EMB (CTAF, 2006).

In 2010, the CTAF conducted a systematic re-review of available published evidence focusing on results of the AlloMap test which included six observational studies and one randomized trial. Three of the publications included in this review reported on subsets of participants from the CARGO trial, as well as results of the IMAGE trial and concluded that, "This technology meets CTAF's assessment criteria for safety, effectiveness and improvement in health outcomes when used to manage HT patients at least one year post-transplant." The CTAF assessment included the following conclusions:

> The AlloMap gene expression profile has a high negative predictive value, but a low positive predictive value. Thus, it may be useful to avoid biopsy in stable patients, but the high false positive rate precludes its use to definitively diagnose acute cellular rejection. Endomyocardial biopsies will still need to be performed in all patients with elevated AlloMap scores and all patients with clinical signs of rejection. The IMAGE trial provides data supporting the non-inferiority of a monitoring strategy for heart transplant patients incorporating the AlloMap gene expression profile in lieu of routine endomyocardial biopsy. However, the data only support such strategies in patients more than

> a year post-transplant. More data are needed to confirm the tests utility earlier in the post-transplant period when the majority of endomyocardial biopsies are performed (CTAF/Tice, 2010).

In 2011, the Blue Cross Blue Shield Association published a Technology Assessment Report of GEP as a noninvasive method to monitor for cardiac allograft rejection. This review and analysis of the available published evidence concluded that the use of GEP as a noninvasive method to monitor for cardiac allograft rejection does not meet the TEC criteria. The following are some summarized conclusions:

> Although a higher score is associated with a greater likelihood of rejection class 3A or higher, the diagnostic characteristics of AlloMap® testing are uncertain. Study methods are unclear, study samples are incompletely described, numbers of cases of rejection are apparently small, and cutoff scores appear to have been determined post hoc. The sensitivity of the test for detecting rejection is uncertain (TEC, 2011).

Definitions

Allograft rejection, also referred to as acute cellular rejection (ACR): The recipient's immune system rejects the donor heart.

Endomyocardium: The innermost lining of the heart.

Endomyocardial biopsy (EMB): A tissue sample of the endomyocardium.

Heart transplant (HT): Removal of a human heart and replacing it with a donor heart.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

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 AlloMap®, CareDx, Inc.

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:
For the procedure code listed above when criteria are not met.

When services are also Investigational and Not Medically Necessary:
For the procedure code listed below in all instances, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

84999	Unlisted chemistry procedure [when specified as breath test for heart transplant rejection (Heartsbreath test)]

ICD-10 Diagnosis

All diagnoses

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AlloMap
Breath Test as an Aid for Diagnosis of Heart Transplant Rejection
Gene Expression Molecular Profiling
Heartsbreath

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. References were updated.
	12/16/2020	Updated Coding section with 01/01/2021 CPT changes; added 84999 replacing 0085T deleted 12/31/2020.
Reviewed	02/20/2020	MPTAC review. References were updated.
Reviewed	03/21/2019	MPTAC review. References were updated.
Reviewed	05/03/2018	MPTAC review. The document header wording was updated from "Current Effective Date" to "Publish Date." References were updated.
Reviewed	05/04/2017	MPTAC review. The Rationale and References sections were updated.
Reviewed	05/05/2016	MPTAC review. References were updated.
	01/01/2016	Updated Coding section with 01/01/2016 CPT changes; removed ICD-9 codes.
Reviewed	05/07/2015	MPTAC review. References were updated.
Reviewed	05/15/2014	MPTAC review. The Rationale and References were updated.
Reviewed	05/09/2013	MPTAC review. References were updated.
Reviewed	05/10/2012	MPTAC review. The Background and References were updated.
Revised	05/19/2011	MPTAC review. The position on AlloMap molecular expression testing has been changed to now consider medically necessary when criteria are met. The Rationale, Background, Coding and Reference sections were updated.
Reviewed	05/13/2010	MPTAC review. The Background and Reference sections were updated.
Reviewed	05/21/2009	MPTAC review. Updated Reference section.
Reviewed	05/15/2008	MPTAC review. References were updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. Reference section was updated.
Reviewed	06/08/2006	MPTAC review. References were updated and information was added about the CARGO Study of AlloMap testing.
Revised	07/14/2005	MPTAC review. AlloMap® molecular testing added as investigational/not medically necessary.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title

Anthem, Inc. WellPoint Health Networks, Inc.	12/02/2004	2.04.32	No prior document Breath Test for Use as an Aid in the Diagnosis of Heart Transplant Rejection