Healthy Blue

# Medical Policy

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| **Subject:** | Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection | | |
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## Description/Scope

This document addresses 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. Additional tests include AlloSure® Heart, myTAI$_{HEART}$ cell free DNA (cfDNA), MMDx Heart and others.

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.

Additional noninvasive tests for detection of heart transplant rejection are considered **investigational and not medically necessary** including, but not limited, to AlloSure Heart, AlloSeq cell-free DNA, MMDx Heart and myTAI$_{Heart}$.

## Rationale

**AlloMap Molecular Expression Testing**

In 2008, FDA 510(k) clearance as a Class II approval was granted for AlloMap Molecular Expression Testing (CareDx, Inc., Brisbane, CA) as an in-vitro, diagnostic, multivariate, index assay of 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 endomyocardial biopsies (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.

The Cardiac Allograft Rejection Gene Expression Observation Study (CARGO) investigated these patterns of gene expression detected in peripheral blood by the AlloMap testing. CARGO included eight U.S. cardiac transplant centers and 650 heart transplant (HT) recipients. Results of CARGO have appeared in abstracts presented at the 2005 annual meeting of the International Society for Heart and Lung Transplantation (ISHLT). While the results were promising, the data were considered inadequate to permit firm scientific conclusions regarding how this test will impact the management of HT recipients (Deng, 2006).

Subsequent validation studies and sub-study analyses of the CARGO results provide additional data regarding the potential utility of the AlloMap test in detecting transplant rejection (Bernstein, 2007; Mehra, 2007b; Mehra, 2008). More recent results of CARGO and the CARGO II trial reflect similar results. CARGO II was a European observational study to further validate AlloMap's gene expression profiling (GEP) test performance. For greater than or equal to 2 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). Trial investigators propose that the low prevalence of ACR contributed to the high negative predictive value (NPV) and limited positive predictive value (PPV) of GEP testing. They concluded that the 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).

The Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial was published in 2010. This was a was a randomized, event-driven, noninferiority trial sponsored by the manufacturer of AlloMap (XDx, Inc.). IMAGE 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 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 monitoring for rejection with 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. 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, the authors concluded that GEP of peripheral blood specimens may offer a reasonable alternative to routine EMB 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 2015, results of another comparative trial were published. The EIMAGE trial (Comparison of AlloMap Molecular Testing and Traditional Biopsy-based Surveillance for Heart Transplant Rejection Early Post-transplantation) was a single-center trial where 60 subjects were randomized to GEP with AlloMap or EMB started at 55 days post HT to examine results of both tests for evidence of ACR in the first year post HT. A positive GEP ≥ 30 between 2 and 6 months, or ≥ 34 after 6 months, prompted a follow-up biopsy. The primary endpoint included a composite of death/retransplant, rejection with hemodynamic compromise or graft dysfunction at 18 months post transplant. A coprimary endpoint included change in first-year maximal intimal thickness by intravascular ultrasound, which is a recognized surrogate for long-term outcome. The composite endpoint was similar between the AlloMap GEP and EMB groups (10% vs 17%; log-rank p=0.44). The coprimary endpoint of first-year intravascular ultrasound change demonstrated no difference in mean maximal intimal thickness (0.35 ± 0.36 vs 0.36 ± 0.26 mm; p=0.944). Steroid weaning was successful in both groups (91% vs 95%). The authors concluded that, in this pilot study, AlloMap GEP starting at 55 days post transplant seems comparable to EMB for rejection surveillance in selected HT recipients and does not result in increased adverse outcomes. However, it was noted that this study was underpowered to determine firm conclusions, and larger randomized trials are needed to confirm these findings (Kobashigawa, 2015).

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).

Current ISHLT recommendations for the use of AlloMap in limited clinical protocols reflect the results of the IMAGE trial. 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.

**Breath testing**

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, generating 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. The device then analyzes the VOCs in alveolar and room air and uses a proprietary algorithm to predict the probability of Grade 3 HT rejection.

The Heartsbreath test should not be used for individuals who have received an HT more than 1 year ago, or for those who 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 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 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%; PPV 5.6%; 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.

**AlloSure Heart and other donor-derived cell free DNA (dd-cfDNA)**

Elevated levels of donor-derived cell free DNA (dd-cfDNA) are shed from the donor graft and associated with transplanted organ injury and rejection (Grskovic, 2016; Khush, 2019). The AlloSure Heart test (CareDx, Inc. Brisbane, CA) has been promoted as a noninvasive alternative to EMB as early as 14 days post transplant. This is a next generation sequencing (NGS)-based assay that quantifies dd-cfDNA relative to the total amount of cfDNA derived from a plasma sample. It uses single-nucleotide polymorphisms (SNPs) to quantify dd-cfDNA in transplant recipients without requiring separate genotyping of the donor and recipient. Test results represent the percent of dd-cfDNA in the total cfDNA in an HT recipient. Changes in the percentage of dd-cfDNA over time provide further evaluation for HT rejection. This plasma test is only performed at a single CareDx CLIA laboratory. Results are expected to be reported within 3 days of blood draw. Early studies have consistently shown a correlation between elevated levels of cfDNA and organ rejection or cellular graft injury (Macher, 2019).

Clinical validity was investigated in two observational prospective studies, the Utility of Donor-Derived Cell Free DNA in Association with Gene Expression Profiling (D-OAR; NCT02178943) and the Cedars-Sinai single-center study. The D-OAR trial included 740 HT recipients at 26 transplant centers in the U.S. Plasma dd-cfDNA was quantified by using targeted amplification and sequencing of a single nucleotide polymorphism panel. The dd-cfDNA levels were correlated to paired events of biopsy-based diagnosis of rejection. The median dd-cfDNA was 0.07% in reference HT recipients (2164 samples) and 0.17% in samples classified as acute rejection (35 samples; p=.005). At a 0.2% threshold, dd-cfDNA had a 44% sensitivity to detect rejection and a 97% NPV. The Cedars-Sinai cohort study of 33 HT recipients considered at high risk for antibody-mediated rejection (AMR) found dd-cfDNA levels were elevated 3-fold in AMR compared with patients without AMR (99 samples; p=.004). The authors concluded that reported test performance characteristics will guide the next stage of clinical utility studies of the dd-cfDNA assay (Khush, 2019).

Knight and colleagues conducted a systematic review of the literature for the use of cfDNA in monitoring of graft health after solid organ transplant (SOT). Electronic databases were searched for studies relating cfDNA fraction or

levels to clinical outcomes, and data including measures of diagnostic test accuracy were extracted. Narrative analysis was performed. Ninety-five articles from 47 studies met the inclusion criteria (18 kidneys, 7 livers, 11 hearts, 1 kidney-pancreas, 5 lungs, and 5 multiorgans). The majority were retrospective and prospective cohort studies, with 19 reporting diagnostic test accuracy data. Multiple techniques for measuring dd-cfDNA were reported, including many not requiring a donor sample. It was noted that dd-cfDNA falls rapidly within 2 weeks post transplant and that baseline levels vary by organ type. Levels are elevated in the presence of allograft injury, including acute rejection and infection and return to baseline after successful treatment. Elevation of cfDNA levels is seen in advance of clinically apparent organ injury. Discriminatory power was greatest for higher grades of T cell-mediated and antibody-mediated acute rejection, with high NPVs. The authors noted that cfDNA is a promising biomarker for monitoring the health of SOTs. Future study is needed to define clinical utility and benefit in routine prospective monitoring following SOT (Knight, 2019).

The myTAI$_{HEART}$ (TAI Diagnostics, Inc., Milwaukee, WI) is another laboratory-developed test that measures dd-cfDNA in blood plasma as a marker for ACR and transplanted organ injury. This test is conducted exclusively at the TAI Diagnostics clinical reference laboratory with proprietary software using quantitative PCR genotyping to predict risk for ACR. It is proposed for use in HT recipients 2 months of age or older at least 1 week post HT (TAI, 2018). To date, observational studies with small sample size have suggested that dd-cfDNA monitoring of HT recipients may be a useful tool to detect and probably anticipate ACR (North, 2020). Further study is needed to inform about how test results should be interpreted in the context of the individual's total clinical findings, history and other test results. TAI Diagnostics reported temporary suspension of production of the myTAI$_{HEART}$ test in 2020. Production has not resumed at the time of this update.

**Additional non-invasive tests**

AlloSeq® cfDNA (CareDx Inc. Brisbane, CA) also measures dd-cfDNA utilizing low DNA input, NGS technology, and streamlined analysis to assist in improved transplant surveillance. To date, this test is being used for research purposes only.

The Presage® $ST_2$ assay (soluble suppression of tumorigenicity-2) (Critical Diagnostics, San Diego, CA) in serum is another noninvasive test which has been cleared by the FDA for use in the prognostic evaluation of chronic heart failure (HF). It has also been suggested for use as a prognostic biomarker post HT as a predictor of AMR (graft-versus-host disease). To date, published evidence has been limited to a few retrospective observational studies. Large well designed trials are needed (Januzzi, 2013; Pascual-Figal, 2011).

The Molecular Microscope® MMDx—Heart (Kashi Clinical Laboratories, Portland, OR) is a microarray-based system that utilizes microRNA profiling (mRNA gene expression analysis) to assess EMB specimens following HT. It is proposed for use in prognostic evaluations for AMR. Further validation is needed in large well designed trials to confirm initial favorable findings (Halloran, 2017).

The Viracor TRAC® Heart dd-cfDNA (Viracor Eurofins, Inc. Lee's Summit, MO) is another assay that uses NGS to determine the percentage of circulating cfDNA in transplant recipients. The cfDNA is extracted from plasma isolated from whole blood. NGS and genome-wide recipient genotype data are then analyzed by a bioinformatics pipeline that calculates the percentage of dd-cfDNA present. This is proposed to correlate with allograft injury due

to rejection. To date, this test has not been cleared for diagnostic use by the FDA. This test is not suitable for use during pregnancy, if the donor and recipient are identical twins, if the individual has received multiple transplants from different donors, or if the donor and recipient are siblings from a consanguineous marriage. According to the manufacturer, these clinical situations will cause the bioinformatics pipeline to generate an inaccurate result.

In summary, published scientific information does not show that use of laboratory tests, other than AlloMap molecular profiling testing, leads to improved health outcomes in clinical practice.

## Background/Overview

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.

According to a scientific statement about newer tests for HT rejection from the American Heart Association, the following is noted:

> Standardization of management strategies for AMR is lacking in large part because of the absence of clinical trials that prospectively evaluate therapies for AMR. The definition of AMR is also in flux as more sensitive diagnostic modalities become available. Although the currently available gene expression profile test for rejection (Allomap) is useful in the prediction of ACR, there is evidence that the fraction of circulating cell-free donor DNA may be useful in detecting both ACR and AMR (Colvin, 2015).

***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).

## Definitions

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

Antibody-mediated rejection (AMR): Refers to all allograft rejection caused by antibodies directed against donor-specific HLA molecules, blood group antigen (ABO)-isoagglutinins, or endothelial cell antigens. Antibody-mediated rejection causes chronic graft failure which is typically resistant to therapy and carries an ominous prognosis for the graft.

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**

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| 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<br>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 codes listed below, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

**CPT**

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| 0055U | Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma<br>myTAIHEART, TAI Diagnostics, Inc, TAI Diagnostics, Inc |
| 0087U | Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score<br>Molecular Microscope® MMDx—Heart, Kashi Clinical Laboratories |

| | |
|---|---|
| 0118U | Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA [when specified for heart transplant rejection] Viracor TRAC™ dd-cfDNA, Viracor Eurofins, Viracor Eurofins |
| 81479 | Unlisted molecular pathology procedure [when specified as testing for heart transplant rejection, such as Allosure Heart, AlloSeq cfDNA, Presage ST2] |
| 81599 | Unlisted multianalyte assay with algorithmic analysis [when specified as testing for heart transplant rejection] |
| 84999 | Unlisted chemistry procedure [when specified as breath test for heart transplant rejection (Heartsbreath test)] |

**ICD-10 Diagnosis**

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| T86.20-T86.298 | Complications of heart transplant |
| Z48.21 | Encounter for aftercare following heart transplant |
| Z94.1 | Heart transplant status |

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Viracor TRAC Heart dd-cfDNA

**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 |
|---|---|---|

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| Reviewed | 11/10/2022 | Medical Policy & Technology Assessment Committee (MPTAC) review. The References were updated. |
| Reviewed | 11/11/2021 | MPTAC review. The Rationale was updated. |
| Revised | 05/13/2021 | MPTAC review. A statement was added for other noninvasive tests considered INV and NMN. The Rationale, Background, Definitions, References and Index were updated. Updated Coding section; added 0055U, 0087U, 0118U and 81479, 81599 NOC. |
| Reviewed | 02/11/2021 | 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. | | | No prior document |
| WellPoint Health Networks, Inc. | 12/02/2004 | 2.04.32 | Breath Test for Use as an Aid in the Diagnosis of Heart Transplant Rejection |