



# 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 Genetic Expression Profiles for Detection of Heart Transplantation Rejection (e.g., AlloMap®)**

**Effective Date ..... 2/15/2011**  
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**Coverage Policy Number ..... 0465**

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## Hyperlink to Related Coverage Policies

- Breath Test for Detection of Heart Transplantation Rejection
- Cardiovascular Magnetic Resonance (CMR) Heart Transplantation

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA does not cover genetic expression profiles (e.g., AlloMap®) to aid in the detection and/or management of heart transplantation rejection because it is considered experimental, investigational or unproven.**

## General Background

Heart transplantation is the treatment of choice in selected patients with end-stage heart failure. The first year after transplantation is the most critical in terms of rejection. Although the risk of rejection decreases over time, late rejection does occur. The current standard for identifying rejection is the endomyocardial biopsy (EMB). Using the International Society for Heart and Lung Transplantation (ISHLT) grading system, EMB samples can be classified as no rejection to severe rejection, which helps to establish and maintain the management of patients following transplantation. While published data evaluating the accuracy of EMB are lacking, no other proposed modalities for detecting rejection (e.g., echocardiography, magnetic resonance imaging, breath testing) have proven to be as accurate or clinically useful as EMB.

EMBs are initially performed weekly and then at increasing intervals. At 12 to 24 months following transplantation, EMB may be performed every three to six months. The biopsy is necessary because rejection may not manifest any clinical signs or symptoms. However, the procedure is not without limitations. It is painful, invasive and does not detect rejection until it is actually present. Biopsy specimens may be difficult to obtain

and/or inadequate due to poor venous access. Tissue samples may also be obscured by scarring. Reported complications of EMB include: hematoma, infection, arrhythmia, ventricular perforation, and fistulas. EMB is reported to be limited by suboptimal interobserver reproducibility and uniform interpretation, and there may be a lack of histological findings in patients with hemodynamic compromise (Mehra and Parameshwar, 2010; Cadeiras, et al., 2007; Fang, 2007; Renlund, et al., 2007; Patel and Kobashigawa, 2006; Starling, et al., 2006; Mehra, 2005). The limitations of EMB have prompted researchers to develop alternatives.

AlloMap<sup>®</sup>, a proposed alternative to EMB, is a blood test in which gene expression is measured by quantifying the gene-specific messenger RNA (mRNA) that is present in the sample. The expression level of 20 genes is measured using quantitative real-time polymerase chain reaction (qRT-PCR). The results are reported as an integer ranging from 0–40, and the lower the score the less the likelihood that the patient will experience rejection (i.e., AlloMap detects a low risk of rejection). It is proposed that circulating peripheral blood mononuclear cells may be indicative of rejection earlier than changes seen at local sites.

Using AlloMap to detect patients who are at low risk for acute cellular rejection is proposed to decrease the need for frequent endomyocardial biopsies. The test is recommended for use in conjunction with standard clinical evaluation and assessment (e.g., history and physical, echocardiography, endomyocardial biopsy) of graft function. It is noted that EMB and AlloMap testing complement each other in that the biopsy reveals cellular infiltrate and tissue injury or necrosis, while gene expression represents molecular events of immune and counter-regulatory signal activation. The AlloMap test has not been validated for use in patients who demonstrate antibody-mediated rejection or noncellular rejection accompanied by hemodynamic compromise, pregnant women, patients who have recently (i.e., less than 30 days) received a blood transfusion, patients recently (i.e., less than 20 days) treated with high-dose steroids, patients recently treated for rejection, or patients who are being treated with  $\geq 20$  milligrams per day of prednisone or equivalent (Cadeiras, et al., 2007; Mehra and Uber, 2007). The role of genetic expression profiles (e.g., AlloMap) for the detection of rejection following heart transplantation is still being investigated. This testing is not an established adjunct or alternative for EMB.

#### **U. S. Food and Drug Administration (FDA)**

In 2008, XDx Laboratories received 510(k) Class II approval for AlloMap Molecular Expression Testing “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 ( $\geq 55$  days) post-transplantation (FDA, Nov 2008).

#### **Literature Review**

There is insufficient evidence in the published peer-reviewed literature to support the clinical utility of genetic expression profiles (e.g., AlloMap) for the detection of rejection following heart transplantation. Studies evaluating the use of this testing compared to EMB are lacking.

Scientists at XDx and investigators from eight cardiac transplant centers in the United States designed and conducted the CARGO (Cardiac Allograft Rejection Gene Expression Observational) Study to determine if monitoring for rejection using gene expression profiling could be developed (Deng, et al., 2006). It was hypothesized that recirculating peripheral blood mononuclear cells (PBMC) may reflect earlier signs of rejection than those at local sites, and measurement of PBMC could possibly replace the need for frequent EMB in asymptomatic patients. The study tested the hypothesis that “a gene expression test could discriminate International Society for Heart and Lung Transplantation (ISHLT) grade 0 rejection (quiescence) from moderate/severe (ISHLT grade  $\geq 3A$ ) rejection (nonquiescence)”. This multicenter, observational study was conducted in three phases: candidate gene discovery (n=285 rejection and quiescent samples from 98 patients), diagnostic development (n=36 rejection samples from 28 patients and 109 quiescent samples from 86 patients), and validation (n=31 rejection and 32 quiescent samples from 63 patients). Routine patient monitoring was conducted utilizing EMB, hemodynamic and/or echocardiography, immunosuppression, laboratory testing, and tracking of complications. Data were also obtained from samples not used in the three phases to estimate the negative predictive value (NPV) and positive predictive value (PPV) of this patient population. An 11 gene real-time test was derived and converted to a score of 0–40, which was validated in an independent set (n=31 rejections; 32 quiescent samples). The study distinguished between moderate/severe rejection and quiescence with an 83.9% agreement with grade ISHLT  $\geq 3A$  rejection at a defined threshold score of 20 (scores  $\geq 20$  indicate rejection). The agreement for correctly classifying the quiescence samples was 37.5%. A secondary

validation, including the 63 previously tested samples (n=62 rejections; 122 quiescent), was reported at 75.8% for rejections and 41.8% for quiescent samples. At a threshold of 30, the estimated positive predictive value was 6.8% and the negative predictive value was 68%. Results determined that a test including a combination of 11 genes could detect the absence of rejection. The 11 gene test predicted that patients with low molecular scores at or after one year following transplant were at low risk of current moderate/severe rejection (NPV > 99%). The authors stated, that although the primary endpoint was achieved, "important technical and clinical limitations of the study would have to be addressed to further evaluate the clinical role of this approach." According to the authors, the limitations of the study included: (1) episodes of mild rejection on biopsy cannot be ruled out by the test; (2) the test has a low positive predictor value relative to biopsy; (3) a nonquiescent score requires full workup, including EMB to differentiate types of rejection; (4) the impact of infections on the test are not known; and (5) the study does not address the predictive capacity of molecular testing for future rejection.

Bernstein et al. (2007) conducted a subanalysis of the CARGO study to determine if gene expression (GE) (i.e., AlloMap genetic testing) could distinguish different forms of mild heart transplant rejection. Inclusion criteria were met by 265 of the 737 adult and pediatric CARGO patients. Reinterpretation of the tissue identified: 176 grade 0 biopsies, 17 grade 1As, 12 grade 1Bs, 21 grade 2, and 24 grade 3As. The mean GE scores differentiated moderate-to-severe rejection (grades  $\geq$  3A) ( $32 \pm 0.9$ ) from grades 0 ( $25.3 \pm 0.5$ ), 1A ( $23.8 \pm 2.1$ ) and 2 ( $26.9 \pm 1.5$ ) ( $p < 0.00001$ ,  $p < 0.001$  and  $p < 0.01$ , respectively). The mean GE score for grade 1B was indistinguishable from that for grades  $\geq$  3A, ( $29.8 \pm 2.0$  vs.  $32.0 \pm 0.9$ ) ( $p = 0.25$ ). Based on a calculation of the fold-difference of each gene, grade 1B was identified as a subgroup of rejection with a peripheral gene expression profile that more closely resembled moderate-to-severe rejection. The study also analyzed whether or not the time from transplantation influenced the GE scores compared to the grades. For the two- to six-month period following transplantation, the mean GE score for grade  $\geq$  3A ( $30.8 \pm 1.4$ ) was not significantly different from that for grade 1B ( $28.5 \pm 3.9$ ) ( $p = 0.49$ ). The mean GE scores differentiated grades 0, 1A, and 2 from grades  $\geq$  3A. EMBs obtained more than six months following transplantation indicated grades  $\geq$  3A demonstrated mean GE scores similar to grade 1B scores ( $p = 0.19$ ). Mean GE scores for grades 0, 1A, and 2 were significantly lower than for grades  $\geq$  3A scores. The authors noted that the use of post hoc analysis of the CARGO study data "introduced potential limitations to the interpretation of these data." They also noted that since there were no additional biopsy interpretations for the subanalysis, a smaller number of panel-confirmed grades were available for analyses. They concluded that the "clinical relevance of these data remains to be defined."

Mehra et al. (2007) also conducted a subanalysis of cardiac allograft recipients (n=104) from the CARGO study to determine if the AlloMap test could distinguish between rejection-free stable patients and patients who develop Grade  $\geq$  3A rejection within 12 weeks following transplantation. In addition, the study characterized the associations with rejection within 180 days of transplantation, identified individual classifier genes' associated with the risk of future rejection and explored the pathways and functions of the genes. Patients with grades 0 or 1A at baseline and free of  $\geq$  grade 2 rejection for at least the first 12 weeks post-transplantation were designated as the matched control group (n=65). The rejection group included 39 patients, clinically stable at baseline, who experienced an episode of grade  $\geq$  3A within 12 weeks following sample collection. Data for the study was analyzed from blood samples and EMB obtained during the same visit. Analysis of the data demonstrated a significant difference in the mean GE score of  $27.4 \pm 6.3$  for the study group and  $23.9 \pm 7.1$  for the control group ( $p = 0.01$ ). The study also analyzed a subgroup of these patients who were  $\leq$  180 days post-transplant and reported a significant difference in the mean GE score of  $28.4 \pm 4.9$  for the study group (n=28) and  $22.4 \pm 7.5$  for the control group (n=46) ( $p < 0.001$ ). The relative expression of each classifier gene was compared between the study group and the control group, and the data demonstrated that "transcriptional signals of genes regulated by corticosteroids or involved in T-cell activation in peripheral blood of heart transplant recipients are associated with the presence or absence of future clinically relevant rejection." The authors stated that the data from this study "must be interpreted with care and in the context of the case-control study in which they were derived." They further explained that case-control studies include "inherent spectrum bias, preventing generalization," and noted that milder rejection grades (i.e., 1B and 2) were not addressed.

In 2007, Yamani et al. conducted two retrospective reviews. The first study (Apr 2007a) included 69 patients and evaluated the impact of transplant coronary allograft vasculopathy (CAV) on AlloMap gene expression analysis. Evidence of CAV within  $4.3 \pm 3$  months of AlloMap testing was demonstrated in 20 patients by coronary angiography. The control group had a mean AlloMap score of  $26.1 \pm 6.5$  compared to  $> 32.2 \pm 3.9$  in the CAV group ( $p < 0.001$ ). Fifteen control patients and 14 CAV patients had an AlloMap score of greater than 30 ( $p = 0.0026$ ). CAV was associated with a significantly increased AlloMap score in the absence of significant

rejection ( $p=0.0002$ ). The second review (2007b) investigated the impact of early post-transfusion ischemic injury on subsequent AlloMap testing from data retrieved from a transplant database ( $n=67$ ). The subjects were evaluated at a mean  $34 \pm 20$  months following heart transplantation. Compared to the control group, the injury group demonstrated worse five-year freedom from vasculopathy, lower left ventricular ejection fraction (LVEF), and higher percentage of AlloMap scores. The presence of ischemic injury was associated with a significant increase in AlloMap scores ( $p<0.0001$ ).

As a follow-up analysis to the CARGO study, Mehra et al. (2008) sought to determine how peripheral blood transcriptional profiling signature using AlloMap might perform in the setting of a more representative patient population (i.e., estimate of a clinical population) using CARGO samples ( $n=127$ ) of patients who progressed to all grades of histologic rejection. The study also characterized longitudinal serial alterations in the gene expression profile before, during, and after recovery from transplant rejection. For the study group, samples were randomly selected from patients who developed ISHLT Grade  $\geq 3A$  rejection within the first 12 weeks following transplantation. The gene expression profiles used for analysis included: 28 rejection patients who progressed to ISHLT grade  $\geq 3A$ , 53 intermediate rejection patients who progressed to ISHLT Grade 1B or 2, and 46 control patients who remained rejection free (Grade 0–1A) at  $\leq 180$  days post-transplant. An AlloMap score of  $\leq 20$  was reported in low risk rejection patients in the first 12 weeks following transplant. None of the low risk patients, 16 of the intermediate group patients, and 13 of the control group patients had a score  $\leq 20$  and did not progress to ISHLT Grade  $\geq 3A$ . In 58% of the cases with an AlloMap score  $\geq 30$ , the patients progressed to severe rejection. “Longitudinal gene expression analysis demonstrated that baseline scores were significantly higher for those who went on to reject, remained high during an episode of rejection, and dropped post-treatment for rejection ( $p<0.01$ )”. The use of AlloMap allowed for the identification and separation of patients into low-, intermediate-, and high-risk groups. However, the results of the study need to be validated in randomized controlled trials with large patient populations to determine the clinical significance of these findings.

Pham et al. (2010a; 2010b) conducted a multicenter ( $n=13$ ), randomized controlled trial (Invasive Monitoring Attenuation through Gene Expression [IMAGE]) ( $n=602$ ) to compare outcomes of monitoring for rejection following heart transplantation using AlloMap gene-testing ( $n=297$ ) compared to routine endomyocardial biopsy ( $n=305$ ). The trial was conducted to test the hypothesis that monitoring for rejection with AlloMap was not inferior to monitoring with routine biopsies with respect to a composite outcome of rejection with hemodynamic compromise, graft dysfunction due to other causes, and death or retransplantation. Non-consecutive patients were selected for the study and some eligible patients were excluded if biopsy-based monitoring was preferred by the treating physician. Patients were age 18 years or older, one to five years post transplantation, clinically stable, and had a left ventricular ejection fraction of 45% or greater. Two years into the study the protocol was expanded to include patients who were six months post transplantation to facilitate enrollment, and the threshold for biopsy was changed from a gene score of 30 to 34 to minimize the number of required biopsies in the AlloMap group. Patients were randomized according to the study center and the interval since transplantation (i.e., 6–12 months [ $n=87$ ], 1–3 years [ $n=413$ ], 4–5 years [ $n=102$ ]). Monitoring was performed according to each centers protocol. Follow-up occurred for 24 months, or until death, or until the study ended (median follow-up 19 months). There were no significant differences in monitoring for rejection by the primary outcomes using AlloMap vs. biopsy ( $p=0.86$ ). There were no statistically significant differences between the two groups in the overall intensity of immunosuppression, mean levels of calcineurin inhibitor, or mean serum creatinine ( $p=0.95$ ). There were 409 biopsies performed in the AlloMap group compared to 1249 in the biopsy group (0.5 biopsies per year vs. 3.0 biopsies per year, respectively), which was statistically significant ( $p<0.0001$ ). Of the 265 biopsies performed due to an AlloMap score of  $\geq 34$ , 143 (54%) revealed no evidence of rejection. Thirty-four AlloMap patients compared to 47 biopsy patients were treated for rejection. Six of the 34 AlloMap rejections were diagnosed by biopsies performed because of an elevated gene score. The remaining 28 were diagnosed by biopsy, clinical symptoms, or echocardiogram. In the biopsy group, 22 episodes of rejection were diagnosed by biopsy alone. The overall death rate did not differ significantly between the two groups ( $p=0.82$ ). Four biopsy complications occurred in the biopsy group and one in the AlloMap group. Patient surveys ( $n=153$  AlloMap and 155 biopsy patients) reported a higher level of satisfaction in the AlloMap group ( $p<0.001$ ). Author-noted limitations of the study included: the short term follow-up; patients less than six months post transplantation were excluded; only 20% of eligible patients were enrolled in the study showing preferential recruitment; since patient selection was biased toward low-risk patients generalizability of the outcome is limited; the lack of blinding may have influenced the intensity of immunosuppression therapy in the AlloMap group; the reduced power of the trial did not exclude the possibility of a 33% decrease in the primary event rates or of a 68% increase risk in the gene-profiling group; and the limited power of the study did not allow for a firm conclusion to

be reached regarding the use of gene-expression profiling as a substitute for the performance of biopsies. There were 15 AlloMap and 26 biopsy patients excluded from the study.

Following a review of the literature, the California Technology Assessment Forum (CTAF) (2010) concluded that the use of gene expression profiling (i.e., AlloMap) met their technology criterion for safety, effectiveness and improvement in health outcomes when used to manage heart transplant patients who were at least one year post-transplant. They noted that due to AlloMap's high negative predictive value and low positive predictive value, the test may be used to avoid biopsy in stable patients, but the high false positive rates prevent the test from being used to definitely diagnose acute cellular rejection. CTAF stated "patients and treating clinicians need to be informed about the uncertainties surrounding the relative benefits and harms associated with a monitoring strategy that incorporates gene expression profiling".

In a technology report based on gene expression profiling for heart transplant rejection, ECRI (2009) concluded that the "current evidence does not assess how use of gene expression profiling (GEP) to monitor acute heart transplant rejection affects patient outcomes and existing evidence does not support other uses of GEP in this patient population".

### Professional Societies/Organizations

In their 2010 guidelines on the care of heart transplant (HT) recipients, the International Society for Heart and Lung Transplantation stated "gene expression profiling (AlloMap) can be used to rule out the presence of ACR [acute cardiac rejection] of grade 2R [i.e., an infiltrate plus the presence of multifocal myocyte damage] or greater in appropriate low-risk patients, between 6 months and 5 years after HT". This recommendation is based on data from the CARGO and IMAGE clinical trials.

### Summary

Evidence in the published peer-reviewed scientific literature comparing genetic expression profiles such as AlloMap® to endomyocardial biopsy (EMB) is limited. The overall body of evidence is not yet sufficient to draw definitive conclusions regarding the incremental clinical utility of this testing and impact on health outcomes. The available published studies to date have included small patient populations at various post-transplantation periods, precluding the ability to generalize findings. A nonquiescent AlloMap score or any clinical suspicion of rejection requires a full clinical evaluation including EMB. Definitive patient selection criteria have not been established, and there is a lack of consensus on the AlloMap threshold score at which point a biopsy should be performed. Whether the use of genetic expression profiles in the management of heart transplantation patients can reduce the need for invasive endomyocardial biopsy (EMB) is not yet known. While the technology is promising, the role of this testing in the management of heart transplantation patients has not yet been established.

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## Coding/Billing Information

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

**Experimental/Investigational/Unproven/Not Covered when used to report genetic expression profiles (e.g., AlloMap®) for detection of heart transplantation rejection:**

84999	Unlisted chemistry procedure
86849	Unlisted immunology procedure
88299	Unlisted cytogenetic study

ICD-9-CM Diagnosis Codes	Description
996.83	Complications of transplanted organ, heart
V42.1	Organ or tissue replaced by transplant, heart

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

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	02/15/2008	0465	Genetic Expression Profiles for Detection of Heart Transplantation Rejection (e.g., AlloMap <sup>®</sup> )

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