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Coverage Policy

Cigna covers genetic expression profile (i.e., AlloMap®) in lieu of endomyocardial biopsy as medically necessary when ALL of the following criteria are met:

- result will be used to determine the need for subsequent endomyocardial biopsy to clarify rejection status
- age 15 years or older
- six months to five years post-heart transplantation
- heart allograft function is stable as demonstrated by ALL of the following:
  - absence of signs or symptoms of congestive heart failure
  - current echocardiogram with left ventricular ejection fraction (LVEF) ≥ 45%
  - absence of severe cardiac allograft vasculopathy (CAV)
- low probability of moderate or severe acute cellular rejection as demonstrated by BOTH of the following:
  - International Society for Heart and Lung Transplantation [ISHLT] rejection status Grade 0R or 1R on all previous endomyocardial biopsies
  - no history or evidence of antibody mediated rejection
- no history of elevated genetic expression profile (i.e., AlloMap) that prompted subsequent endomyocardial biopsy to clarify rejection status

Cigna does not cover genetic expression profile (i.e., AlloMap) for any other indication 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 (Grade 0R), mild rejection (Grade 1R), moderate rejection (Grade 2R) or severe rejection (Grade 3R). These classifications help 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 (International Society of Heart and Lung Transplantation [ISHLT], 2010).

EMBs are initially performed weekly and then at increasing intervals. At 12 to 24 months following transplantation, EMB may be performed every three to twelve 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® has evolved into an established alternative to EMB in a defined subgroup of heart transplant recipients. The blood test measures gene expression by quantifying the gene-specific messenger RNA (mRNA) that is present in the sample. The expression level of 11 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.

AlloMap may be used to help identify patients, age 15 years or older, who are between one and five years post-heart transplantation, have a stable heart allograft function, and are at low risk of moderate or severe rejection and therefore, may not need to undergo 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.

Stable heart allograft function is determined by the absence of congestive heart failure, left ventricular ejection fraction (LVEF) ≥45% and absence of severe cardiac allograft vasculopathy (CAV)). Symptoms of congestive heart failure include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, syncope, palpitation and/or arrhythmias. LVEF measures the amount of blood being pumped out of the left ventricle of the heart. A LVEF below 45 may be evidence of CHF or cardiomyopathy. Rejection can be associated with hemodynamic compromise as indicated by a decrease in the LVEF. LVEF can be assessed by echocardiography, cardiac catheterization, MRI, multiple gated acquisition (MUGA) scan, or ventriculography (Pharm, et al., 2010; Yamani and Taylor, 2010).

Angiography or intravascular ultrasound (IVUS) is used to assess CAV. The classic feature of CAV is diffuse concentric narrowing with luminal stenosis. CAV may be diagnosed when there is stenosis of 50% within any major epicardial coronary vessel or branches on angiography, severe diffuse or distal vessel tapering on angiography, maximal intimal thickness ≥0.5 mm in any major epicardial coronary vessel at the time of intravascular ultrasound, evidence of recent ischemic injury on biopsy, graft dysfunction and/or an epicardial stenosis of <50% that does not respond to anti-rejection therapy. Pharm, et al. identified severe CAV as >50% left main stenosis; ≥50% stenosis in ≥ 2 primary vessels (proximal 1/3 or middle 1/3 of the left anterior descending or left circumflex, right coronary artery to takeoff of posterior descending artery in right-dominant coronary circulations) or isolated branch stenoses of >50% in all three systems (diagonal branches, obtuse marginal branches, distal 1/3 of left anterior descending or left circumflex, posterior descending artery, posterior
lateral branch, and right coronary artery to takeoff of posterior descending artery in non-dominant systems). Clinical manifestation of CAV may be silent, or occur as acute myocardial infarction, congestive heart failure, arrhythmias, and/or wall motion abnormalities (Pharm, et al., 2010; Yamani and Taylor, 2010; Schmauss and Weis, 2008).

Acute cellular rejection (ACR), or cell-mediated rejection, is the clinical syndrome that occurs as the result of an alloimmune response against a transplanted organ and can be caused by either a cellular or humoral response. ACR is the most common form of rejection and occurs at least once in approximately 50% of heart transplant recipients during the first year. Patients with a low probability of moderate or severe acute cellular rejection have a histological International Society of Heart and Lung Transplantation (ISHLT) grade 0 or grade 1. Typically, these grades are not treated for rejection. Grades 2R (moderate) and 3R (severe) are indicative of rejection and treated per institutional protocol. The two key elements of acute cellular rejection are the presence of lymphocytes and myocyte injury. Low probability of moderate or severe acute cellular rejection has been defined as patients who do not have treatable rejection on two consecutive biopsies over a period of 3–9 months. Treated rejection includes the administration of anti-rejection therapy (e.g., steroids, antibody therapy) (Maleszewski and Burke, 2013; Acker and Jessup, 2011; ISHLT, 2010; Pharm, et al., 2010).

Antibody mediated rejection (AMR), or humoral rejection, is initiated by antibodies rather than by T cells. AMR is manifested as graft dysfunction or hemodynamic compromise (e.g., shock, hypotension, decreased cardiac output, and/or a rise pulmonary capillary wedge pressure) in the absence of cellular rejection on biopsy. The diagnosis is based on histologic findings indicative of acute myocardial capillary injury. Per Pham et al., AMR may be associated with hemodynamic compromise including: “LVEF ≤30% or at least 25% below baseline, cardiac index <2 L/min/m² or administration of inotropic agents to support circulation” (Berry, et al., 2013; Acker and Jessup, 2011; Pham, et al., 2010).

AlloMap has been proposed as an alternative to EMB in patients for whom biopsy is contraindicated or cannot be performed. One complication of biopsy is tricuspid regurgitation caused by repeated passing of the bioptome across the tricuspid valve into the right ventricular to obtain tissue specimens. Repeated biopsies may further damage the valve and increase the regurgitation (Strecker, et al., 2013; Badiwala and Rao, 2007). Other contraindications for EMB include profound hemodynamic compromise, coagulopathy, and mechnical tricuspid prosthesis (Bennett and Tang, 2013). Lack of adequate vascular access, malignant arrhythmic events (e.g., unstable ventricular arrhythmias) or intracavitary mass or thrombus may also be contraindications to EMB. Clinical trials investigating AlloMap in this subset of patients are lacking.

AlloMap 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 ≥20 milligrams per day of prednisode or equivalent (Caideiras, et al., 2007; Mehra and Uber, 2007).

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 (≥55 days) post-transplantation (FDA, Nov 2008).

Literature Review
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 ≥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),
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 ≥ 3A) (32 ± 0.9) from grades 0 (25.3 ± 0.5), 1A (23.8 ± 2.1) and 2 (26.9 ± 1.5) (p<0.0001, p<0.001 and p<0.01, respectively). The mean GE score for grade 1B was indistinguishable from that for grades ≥ 3A, (29.8 ± 2.0 vs. 32.0 ± 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 ≥ 3A (30.8 ± 1.4) was not significantly different from that for grade 1B (28.5 ± 3.9) (p=0.49). The mean GE scores differentiated grades 0, 1A, and 2 from grades ≥ 3A. EMBs obtained more than six months following transplantation indicated grades ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ± 6.3 for the study group and 23.9 ± 7.1 for the control group (p=0.01). The study also analyzed a subgroup of these patients who were ≤ 180 days post-transplant and reported a significant difference in the mean GE score of 28.4 ± 4.9 for the study group (n=28) and 22.4 ± 7.5 for the control group (n=46) (p<0.001). To explore the molecular pathways associated with steroid sensitivity and T-cell activation, the expression levels of 33 additional genes were measured, 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 ± 3 months of AlloMap testing was demonstrated in 20 patients by coronary angiography. The control group had a mean AlloMap score of 26.1 ± 6.5 compared to > 32.2 ± 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 ± 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 ≥ 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 ≥ 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 ≤ 180 days post-transplant. An AlloMap score of ≤ 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 ≤ 20 and did not progress to ISHLT Grade ≥ 3A. In 58% of the cases with an AlloMap score ≥ 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 ≥ 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.

Technology Assessments

BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC): BCBSA (2011) conducted a systematic review of the literature to determine if AlloMap testing improved health outcomes compared to other methods used for monitoring rejection following heart transplantation. Validation studies that only included patients with no rejection or class 3A rejection reported a sensitivity of 76–84% and specificity of 38–41% at a cutoff score of 20. Post hoc analyses of subgroups (n< 30 patients) who were > 6 months or > 12 months post-transplant with higher cutoff scores reported sensitivities of 71.4–80% and specificities of 77.8%–78.7%. Depending on the cutoff score used to denote a positive test, other studies reported a positive predictive value (PPV) typically < 7% and a negative predictive value (NPV) > 98%. According to BCBSA, the data used for these values was not available and the results were not consistent with results from actual patient samples. One study reported a 7.8% PPV and a 100% NPV using a cutoff score of 34 but out of the total 243 samples, only five were rejection samples. The authors reported that higher AlloMap scores were associated with a greater likelihood of rejection in class 3A or higher patients but the “diagnostic characteristics of AlloMap testing were uncertain”, study methods were unclear, study samples were not completely described, number of cases of rejection were small and cutoff scores appeared “to be determined post hoc.” According to BCBSA, the “sensitively of the test for detecting rejection is uncertain.” The available evidence was insufficient to permit conclusions regarding the effects of AlloMap on net health outcomes, or if the test is as beneficial as any established alternatives for monitoring heart transplant patients.

California Technology Assessment Forum (CTAF): Following a review of the literature, 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”.

ECRI Institute: In a technology evidence report on AlloMap, ECRI (2011) was unable to determine the accuracy of AlloMap in predicting an episode of moderate or severe acute cellular rejection (ACR) because its sensitivity and specificity have not been defined. One diagnostic cohort study and one randomized controlled trial met inclusion criteria. The randomized controlled trial compared AlloMap (n=297) to EMB (n=305) in patients six-month to five-years post-transplant (mean follow-up 19 months) and reported a negative predictive value of 98.9% but a positive predictive value of 4.1%. Based on these data, ECRI concluded that AlloMap could be used for identifying patients with a low risk of ACR (i.e., patients with a stable allograft function) but not a high risk of ACR. ECRI pointed out that the number of yearly transplant patients is < 3500 worldwide and a large evidence base would not be expected. Additional research is needed to evaluate the clinical utility of AlloMap in long-term patient rejection surveillance.

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.
Use Outside of the US
Diaxonhip (Paris: ALEHT), a French provider of specialty diagnostic solutions, has entered an agreement with XDx, Inc. to be the exclusive laboratory to perform AlloMap for European heart transplant recipients. For the European market, the AlloMap test will be performed centrally in the Jean Dausset Laboratory, part of the Paris Hospital Group. The test is proposed to be available in selected countries in early 2014 (XDx, 2013).

Summary
Although evidence in the published peer-reviewed scientific literature comparing genetic expression profile (i.e., AlloMap®) to endomyocardial biopsy (EMB) is limited, AlloMap has evolved into an established diagnostic test when used in conjunction with standard clinical evaluation and assessment. The test is used to aid in the identification of a defined subgroup of patients who are at low risk for rejection following heart transplantation. Patients who are one to five year post-transplantation and have stable heart allograft function and low probably of rejection may be a candidate for AlloMap testing in lieu of endomyocardial biopsy.

Coding/Billing Information

Note:
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary when used to report genetic expression profiles (i.e., AlloMap®) for detection of heart transplantation rejection:

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References


