Name of Policy:
Heart Transplant Rejection Laboratory Testing

Policy #: 212       Latest Review Date: June 2016
Category: Laboratory       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Several commercially available laboratory tests assess heart transplant rejection including the Heartsbreath™ test that measures breath markers of oxidative stress, and the AlloMap™ test, which uses gene expression profiling (GEP) to generate a score based on the expression of various immunomodulatory genes. These tests are proposed as alternatives to, or adjuncts to, endomyocardial biopsy, which is invasive.

**Heart Transplant Rejection**
Most cardiac transplant recipients experience at least 1 episode of rejection in the first year after transplantation. In 2005, the International Society for Heart and Lung Transplantation modified its grading scheme for categorizing cardiac allograft rejection. Revised (R) categories are as follows:

- Grade 0R: No rejection
- Grade 1R: Mild rejection (previously Grades 1A, 1B and 2)
- Grade 2R: Moderate rejection (previously Grade 3A)
- Grade 3R: Severe rejection (previously Grades 3B and 4)

Acute cellular rejection is most likely to occur in the first six months, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a lifelong basis, dosing is adjusted based on graft function and the grade of acute cellular rejection determined by histopathology. Endomyocardial biopsies are typically taken from the right ventricle via the jugular vein periodically during the first 6 to 12 months post-transplant. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following six months, and several times (monthly to quarterly) between 6 months and 1 year post-transplant. Surveillance biopsies may also be performed after the first postoperative year e.g., on a quarterly or semiannual basis. This practice, although common, has not been demonstrated to improve transplant outcomes. Some centers no longer routinely perform endomyocardial biopsies after 1 year in patients who are clinically stable.

While endomyocardial biopsy is the criterion standard for assessing heart transplant rejection, it is limited by a high degree of interobserver variability in grading of results and potential morbidity that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy. Finally, biopsy cannot be used to identify patients at risk of rejection, limiting the ability to initiate therapy to interrupt the development of rejection. For these reasons, endomyocardial biopsy is considered a flawed criterion standard by many. Therefore, noninvasive methods of detecting cellular rejection have been explored. It is hoped that noninvasive tests will assist in determining appropriate patient management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false negative and false positive biopsy reports. Two techniques have become commercially available for the detection of heart transplant rejection.

**Noninvasive Heart Transplant Rejection Tests**
The Heartsbreath™ test (Menssana Research, Newark, NJ), a noninvasive test that measures breath markers of oxidative stress, has been developed to assist in the detection of heart rejection.
transplant rejection. In heart transplant recipients, oxidative stress appears to accompany allograft rejection, which degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes that are, in turn excreted as volatile organic compounds in breath. The Heartsbreath test analyzes the breath methylated alkane contour (BMAC), which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes and has been identified as a marker to detect Grade 3 (clinically significant) heart transplant rejection.

Another approach has focused on patterns of gene expression of immunomodulatory cells, as detected in the peripheral blood. For example, microarray technology permits the analysis of the gene expression of thousands of genes, including those with functions that are known or unknown. Patterns of gene expression can then be correlated with known clinical conditions, permitting a selection of a finite number of genes to compose a custom multigene test panel, which then can be evaluated using polymerase chain reaction (PCR) techniques. AlloMap™ (CareDx, Brisbane, CA; formerly XDx, Inc.) is a commercially available molecular expression test that has been developed to detect acute heart transplant rejection or the development of graft dysfunction. The test involves PCR-expression measurement of a panel of genes derived from peripheral blood cells and applies an algorithm to the results. The proprietary algorithm produces a single score that considers the contribution of each gene in the panel. The score ranges from 0 to 40. The Allomap website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cutoff for a positive test. All AlloMap testing is performed at the CareDx reference laboratory in Brisbane, CA.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most of these have had low diagnostic accuracy in diagnosing rejection. Preliminary studies have evaluated the association between heart transplant rejection and micro-RNAs or high-sensitivity cardiac troponin in cross-sectional analyses, but the clinical use has not been evaluated.

Policy:
The measurement of volatile compounds with the Heartsbreath test to assist in the detection of moderate grade 2R/grade 3 heart transplant rejection does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

The use of peripheral blood genetic profiling tests in the management of patients post-heart transplantation, including, but not limited to the detection of acute heart transplant rejection or heart transplant graft dysfunction does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.
Key Points:
The most recent literature update was performed through March 21, 2016. Following is a summary of the key literature to date.

Measurement of Volatile Organic Compounds
The FDA approval of the Heartsbreath test was based on the results of the National Heart Lung and Blood Institute sponsored study entitled Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL study). The HARDBALL study was a 3-year multicenter study of 1,061 breath samples in 539 heart transplant patients. Prior to scheduled endomyocardial biopsy, patient breath was analyzed by gas chromatography and mass spectroscopy for volatile organic compounds. The amount of C4-C20 alkanes and monomethylalkanes was used to derive the marker for rejection known as the BMAC. The BMAC results were compared with subsequent biopsy results, as interpreted by 2 readers using the International Society for Heart and Lung Transplantation (ISHLT) biopsy grading system as the criterion standard or “gold standard” for rejection.

The authors of the HARDBALL study reported that the abundance of breath markers of oxidative stress were significantly greater in grade 0, 1, or 2 rejection than in healthy normal persons. In contrast, in Grade 3 rejection, the abundance of breath markers of oxidative stress was reduced, most likely due to accelerated catabolism of alkanes and methylalkanes that makes up the BMAC. The authors also reported finding that in identifying Grade 3 rejection, the negative predictive value (NPP) of the breath test (97.2%) was similar to endomyocardial biopsy (96.7%) and that the breath test could potentially reduce the total number of biopsies performed to assess for rejection in patients at low risk for Grade 3 rejection. The sensitivity of the breath test was 78.6% versus 42.4% with biopsy. However, the breath test had lower specificity (62.4%) and a lower positive predictive value (PPV) (5.6%) in assessing Grade 3 rejection than biopsy (specificity 97%, PPV 45.2%). In addition, the breath test was not evaluated in Grade 4 rejection.

Findings from the HARDBALL study were published in 2004. No subsequent studies that evaluate use of the Heartsbreath test to assess for graft rejection were identified in literature updates.

Gene Expression Profiling
A 2011 TEC Assessment reviewed the evidence on the use of AlloMap™ testing. The Assessment concluded that the evidence is insufficient to permit conclusions about the effect of the AlloMap™ test on health outcomes. Key evidence in the TEC Assessment and subsequent literature searches is described below.

Analytic
No studies on analytic validity were identified.
Clinical Validity
Patterns of gene expression for development of the AlloMap™ test were studied in the Cardiac Allograft Rejection Gene Expression Observation (CARGO) study, which included eight U.S. cardiac transplant centers enrolling 629 cardiac transplant recipients. The study included discovery and validation phases. In the discovery phase, patient blood samples were obtained at the time of endomyocardial biopsy, and the expression levels of more than 7000 genes known to be involved in immune responses were assayed and compared with the biopsy results. A subset of 252 candidate genes were identified that showed promise as markers that could distinguish transplant rejection from quiescence, and from there, a panel of 11 genes was selected that could be evaluated using polymerase chain reaction (PCR) assays. A proprietary algorithm is applied to the results of the analysis, producing a single score that considers the contribution of each gene in the panel.

The validation phase of the CARGO study, published in 2006, was prospective, blinded, and enrolled 270 patients. Primary validation was conducted using samples from 63 patients independent from discovery phases of the study and enriched for biopsy-proven evidence of rejection. A prospectively defined test cutoff value of 20 resulted in a sensitivity of 84% of patients with moderate/severe rejection but a specificity of 38%. Of note, in the “training set” used in the study, these rates were 80% and 59%, respectively. The authors evaluated the 11-gene expression profile on 281 samples collected at 1 year or more from 166 patients who were representative of the expected distribution of rejection in the target population (and not involved in discovery or validation phases of the study). When a test cutoff of 30 was used, the NPV (no moderate/severe rejection) was 99.6%; however, only 3.2% of specimens had Grade 3 or higher rejection. In this population, grade 1B scores were found to be significantly higher than Grade 0, 1A, and 2 scores but similar to Grade 3 scores.

A second prospective multicenter study, evaluating the clinical validity of GEP with the AlloMap test (CARGO II), was published in 2016. The study enrolled 499 heart transplant recipients who were undergoing surveillance for allograft rejection. The reference standard for rejection status was histologic grade from an endomyocardial biopsy performed on the same day as blood samples were collected. Blood samples needed to be collected 55 days or more post-transplant, more than 30 days after blood transfusion, more than 21 days after administration of prednisone 20 mg/day or more, and more than 60 days after treatment for a prior rejection. Patients had a total of 1579 eligible blood samples for which paired GEP scores and endomyocardial biopsy rejection grades were available.

As in the original CARGO study, the proportion of cases of rejection was small. The prevalence of moderate-to-severe rejection (grade 2R/>3A) reported by local pathologists was 3.2%, which was reduced to 2.0% when confirmation from 1 or more other independent pathologist was required. At a GEP cutoff of 34, for patients who were at least 2 to 6 months post-transplant, the sensitivity of GEP for detecting grade 2R/>3A was 25.0% and the specificity was 88.7%. The PPV and NPV were 4.0% and 98.4%, respectively. Using the same cutoff of 34, for patients more than 6 months post-transplant, the sensitivity of GEP was 25.0% the specificity was 88.8%, the PPV was 4.3% and the NPV was 98.3%. The number of true positives used in the above calculations was 5 (9.1%) of 55 for patients at least 2 to 6 months post-transplant and 6 (10.2%) of 59 for patients more than 6 months post-transplant.
Section Summary: Clinical Validity

The 2 studies (CARGO, CARGO II) examining the diagnostic performance of GEP using the AlloMap testing for detecting moderate/severe rejection are flawed by lack of a consistent threshold for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (i.e., at least 88%), the performance characteristics were calculated based on detection of 10 or fewer cases of rejection each. Moreover, the PPV in the CARGO II study was only 4.0% for patients who were at least 2 to 6 months post-transplant and 4.3% for patients more than 6 months post-transplant.

Clinical Utility

In 2010, results of the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study were published. This was an industry-sponsored noninferiority randomized controlled trial (RCT) that compared outcomes in 602 patients managed with the AlloMap test (n=297) or routine endomyocardial biopsies (n=305). The study was not blinded. The study included adult patients from 13 centers who underwent cardiac transplantation between 1 and 5 years previously, were clinically stable, and had a left ventricular ejection fraction (LVEF) of at least 45%. In order to increase enrollment, the study protocol was later amended to include patients who had undergone transplantation between six months and 1 year earlier; this sub-group ultimately comprised only 15% of the final sample (n=87). Each transplant center used its own protocol for determining the intervals for routine testing. At all sites, patients in both groups underwent clinical and echocardiographic assessments in addition to the assigned surveillance strategy. According to the study protocol, patients underwent biopsy if they had signs or symptoms of rejection or allograft dysfunction at clinic visits (or between visits) or if the echocardiogram showed a LVEF decrease of at least 25% compared to the initial visit. Additionally, patients in the AlloMap group underwent biopsy if their test score was above a specified threshold; however, if they had 2 elevated scores with no evidence of rejection found on 2 previous biopsies, no additional biopsies were required. The AlloMap test score varies from 0 to 40, with higher scores indicating a higher risk of transplant rejection. The investigators initially used 30 as the cutoff for a positive score; the protocol was later amended to use a cutoff of 34 to minimize the number of biopsies needed. Fifteen patients in the AlloMap group and 26 in the biopsy group did not complete the study.

The primary outcome was a composite variable; the first occurrence of 1) rejection with hemodynamic compromise, 2) graft dysfunction due to other causes, 3) death, or 4) retransplantation. The trial was designed to test the noninferiority of gene expression profiling (GEP) with the AlloMap test compared to endomyocardial biopsies with respect to the primary outcome. Use of the AlloMap test was considered noninferior to the biopsy strategy if the one-sided upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) comparing the 2 strategies was less than the prespecified margin of 2.054. The margin was derived using the estimate of a 5% event rate in the biopsy group, taken from published observational studies, and allowing for an event rate of up to 10% in the AlloMap group.

According to Kaplan-Meier analysis, the 2-year event rate was 14.5% in the AlloMap group and 15.3% in the biopsy group. The corresponding HR was 1.04 (95% CI: 0.67 to 1.68). The upper boundary of the CI of the HR, 1.68, fell within the prespecified noninferiority margin (2.054); thus GEP was considered noninferior to endomyocardial biopsy. Median follow-up
was 19 months. The number of patients remaining in the Kaplan-Meier analysis after 300 days was 221 in the biopsy group and 207 in the AlloMap group; the number remaining after 600 days was 137 and 133, respectively. The secondary outcome, death from all-causes at any time during the study, did not differ significantly between groups. There were a total of 13 (6.3%) deaths in the AlloMap group and 12 (5.5%) in the biopsy group (p=0.82). During the follow-up period, there were 34 treated episodes of graft rejection in the AlloMap group. Only 6 of the 34 (18%) patients with rejection presented solely with an elevated AlloMap score. Twenty patients (59%) presented with clinical signs/symptoms and/or graft dysfunction on echocardiogram, and seven patients had an elevated AlloMap score plus clinical signs/symptoms with or without graft dysfunction on echocardiogram. In the biopsy group, 22 patients were detected solely due to an abnormal biopsy.

A total of 409 biopsies were performed in the AlloMap group and 1,249 in the biopsy group. Most of the biopsies in the AlloMap group, 67%, were performed because of elevated gene-profiling scores. Another 17% were performed due to clinical or echocardiographic manifestations of graft dysfunction, and 13% were performed as part of routine follow-up after treatment for rejection. There was 1 (0.3%) adverse event associated with biopsy in the AlloMap group and 4 (1.4%) in the biopsy group. In terms of quality of life, the physical-health and mental-health summary scores of the Short Form Health Survey, 12 were similar in the 2 groups at baseline and did not differ significantly between groups at 2 years.

A limitation of the study was that the threshold for a positive AlloMap test was changed partway through the study; thus, the optimal test cutoff remains unclear. Moreover, the study was not blinded, which could have impacted treatment decisions such as whether or not to recommend biopsy, based on clinical findings. In addition, the study did not include a group that only received clinical and echocardiographic assessment, and therefore, the value of AlloMap testing beyond that of clinical management alone cannot be determined. The uncertain incremental benefit of the AlloMap test is highlighted by the finding that only six of the 34 treated episodes of graft rejection detected during follow-up in the AlloMap group were initially identified due solely to an elevated gene-profiling score. Since 22 episodes of asymptomatic rejection were detected in the biopsy group, it is likely that the AlloMap test is not a sensitive test, possibly missing more than half of the episodes of asymptomatic rejection. Since clinical outcomes were similar in the 2 groups, there are at least 2 possible explanations. The clinical outcome of the study may not be sensitive to missed episodes of rejection, or it is not necessary to treat asymptomatic rejection. In addition, the study was only statistically powered to rule out more than a doubling of the rate of the clinical outcome, which some may believe is an insufficient margin of noninferiority. Finally, only 15% of the final study sample had undergone transplantation less than 1 year before study participation; therefore, findings may not be generalizable to the population of patients 6-12 months post-transplant.

In a follow-up analysis of data from the IMAGE RCT, Deng et al evaluated whether variability in gene expression profiling results were predictive of clinical outcomes. For this analysis, the authors included a subset of 369 patients who had at least two AlloMap tests done before an event or the study end, and at least 1 endomyocardial biopsy and 1 echocardiogram. Patients were included from both arms of the IMAGE RCT. AlloMap test results were expressed in three ways, as an ordinal score from 0 to 39, a threshold score of 1 or 0 depending on whether

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Medical Policy #212
the score was 34 or more or not, and as a variability score, the standard deviation of all of the ordinal scores within a patient. The AlloMap results were entered into a multivariable regression model to predict the composite end point, defined as a patient’s first occurrence of: rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. AlloMap ordinal score and AlloMap threshold score were not predictive of the composite outcome. AlloMap score variability was significantly associated with the composite outcome, with a hazard ratio for a 1-unit increase in variability of 1.76 (95% CI, 1.4 to 2.3). While this study implies that variability in AlloMap score may be a prognostic factor, clinical application of this finding is uncertain.

In 2015, Kobashigawa et al published results of a pilot RCT evaluating the use of the AlloMap test in patients who were 55 days to 6 months posttransplant. The study design was similar to that of the IMAGE RCT: 60 subjects were randomized to rejection monitoring with AlloMap or with endomyocardial biopsy at prespecified intervals of 55 days and 3, 4, 5, 6, 8, 10, and 12 months posttransplant. The threshold for a positive AlloMap test was set at 30 for patients 2 to 6 months posttransplant and 34 for patients after 6 months posttransplant, based on data from the CARGO study. Endomyocardial biopsy outside of the scheduled visits was obtained in either group if there was clinical or echocardiographic evidence of graft dysfunction and for the AlloMap group if the score was above the specified threshold. The incidence of the primary outcome at 18 months posttransplant (composite outcome of first occurrence of death or retransplant, rejection with hemodynamic compromise, or allograft dysfunction due to other causes) did not differ significantly between the AlloMap and biopsy groups (10% vs 17%; p=0.44). The number of biopsy-proven rejection episodes (ISHLT ≥2R) within the first 18 months did not differ significantly between groups (3 in the AlloMap group vs 1 in the biopsy group; p=0.31). Of the rejections in the AlloMap group, 1 was detected after an elevated routine AlloMap test, while 2 were detected after patients presented with hemodynamic compromise. As in the IMAGE study described above, a high proportion of rejection episodes were detected by clinical signs/symptoms (however, this study had only 3 rejection episodes in the AlloMap group).

Section Summary: Clinical Utility
The most direct evidence on the clinical utility of GEP using the AlloMap test comes from a large RCT comparing an AlloMap-directed strategy with an endomyocardial biopsy-directed strategy for detecting rejection, which found that the AlloMap-directed strategy was noninferior. However, given the high proportion of rejection episodes in the AlloMap-directed strategy detected by clinical signs/symptoms, the evidence is insufficient to determine that health outcomes are improved because of the uncertain incremental benefit of the AlloMap test. In addition, a minority of included subjects were in the first year post-transplant. Results from a pilot RCT suggests that AlloMap may have a role in evaluating for heart transplant rejection beginning at 55 days post-transplant, but the study was insufficiently powered to allow firm conclusions about the noninferiority of early AlloMap use.

Summary of Evidence
For individuals who have heart transplant who are tested with measurement of volatile organic compounds to assess allograft rejection, the evidence includes 1 diagnostic accuracy study. Relevant outcomes are overall survival, test accuracy and validity, morbid events, and
hospitalizations. The published study found that, for identifying grade 3 (grade 2R) rejection, the negative predictive value (NPV) of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test 78.6% was better than that for biopsy (42.4%). However, the breath test had lower specificity (62.4%) and a lower positive predictive value (PPV=5.6%) in assessing grade 3 rejection than biopsy (specificity, 97%; PPV=45.2%). The breath test was also not evaluated for grade 4 rejection. This single study is not sufficient to determine the clinical validity of the test measuring volatile organic compounds and no studies on clinical utility were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart transplant who are tested with gene expression profiling (GEP) to assess allograft rejection, the evidence includes 2 diagnostic accuracy studies and several randomized controlled trials (RCTs) evaluating clinical utility. Relevant outcomes are overall survival, test accuracy and validity, morbid events, and hospitalizations. The 2 studies (CARGO, CARGO II) examining the diagnostic performance of GEP for detecting moderate-to-severe rejection lack of a consistent threshold for defining a positive GEP test (i.e., 20, 30, or 34) for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (i.e., at least 88%), the performance characteristics were calculated based on only 10 or fewer cases of rejection so may be imprecise. Moreover, the PPV in CARGO II was only 4.0% for patients who were at least 2 to 6 months post-transplant and 4.3% for patients more than 6 months post-transplant. The clinical utility of GEP compared with routine endomyocardial biopsies has been evaluated in 2 RCTs, the IMAGE study assessing patients more than 6 months post-transplant and a small pilot RCT assessing patients starting at 55 days post-transplant. The threshold indicating a positive test that seems to be currently accepted (a score of 34) was not prespecified; rather it evolved partway through the data collection period in the IMAGE study. In addition, the IMAGE study had several methodologic limitations (e.g., lack of blinding) and it did not determine whether GEP offers incremental benefit over biopsy performed on the basis of clinical exam or echocardiography. Among patients less than 1 year post-transplant, which is the group at highest risk of transplant rejection, there are insufficient data on which to evaluate the clinical utility of GEP. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Positions Statements
In 2010, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients. The guidelines included the following recommendations:

• The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy during the first 6-12 months after transplant for rejection surveillance.
• After the first year post-transplant, EMB surveillance every 4-6 months is recommended for patients at higher risk of late acute rejection.
• Gene Expression Profiling using the AlloMap test can be used to rule out acute heart rejection (Grade 2 or greater) in appropriate low-risk patients between 6 months and 5 years post-transplant.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Key Words:
Heartsbreath test, endomyocardial biopsy, heart transplant rejection, AlloMap™ Test, gene expression profiling, Cardiac Allograft Rejection Gene Expression Observation (CARGO) Study, Invasive Monitoring Attenuation through Gene Expression (IMAGE) Study

Approved by Governing Bodies:
In February 2004, the Heartsbreath test (Menssana Research, Inc.) received approval from the U.S. Food and Drug Administration (FDA) through a Humanitarian Device Exemption. 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 device is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy and is also limited to patients who have had endomyocardial biopsy within the previous month.

In August 2008, AlloMap Molecular Expression Testing (CareDx, Brisbane, CA; formerly XDx, Inc.) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices, in conjunction with clinical assessment, for aiding in the identification of heart transplant recipients with stable allograft function that have a low probability of moderate/severe transplant rejection. It is intended for patients at least 15 years-old who are at least 2 months post-transplant.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
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<tr>
<td>81595</td>
<td>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 (Effective 01/01/16)</td>
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<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
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References:
Policy History:
Medical Policy Group, December 2004 (4)
Medical Policy Administration Committee, January 2005
Available for comment January 21-March 7, 2005
Medical Policy Group, December 2006 (1)
Medical Policy Administration Committee, January 2007
Available for comment January 30-March 8, 2007
Medical Policy Group, September 2007 (3)
Medical Policy Administration Committee October 2007
Medical Policy Group, September 2009 (1)
Medical Policy Group, November 2010 (1): No change in policy statement
Medical Policy Group, April 2012 (1): Update to Key Points and References related to MPP update; no change to policy statement
Medical Policy Panel, April 2013
Medical Policy Group, April 2013 (1): Literature search updated; no change to policy statement
Medical Policy Panel, April 2014
Medical Policy Group, April 2014 (1): Policy statements edited for clarity, no change in coverage or intent; update to Description, Key Points and References; addition of CPT code 86849 related to usage for AlloMap
Medical Policy Panel, April 2015
Medical Policy Group, May 2015 (3): 2015 Updates to Title, Description, Key Points, Governing Bodies, Coding, & References; no change in policy statement; title updated to clarify as Heart Transplant Rejection Laboratory Testing
Medical Policy Group, June 2016 (3): 2016 Updates to Description, Key Points, Policy and References: No change in intent of policy statement-clarifying information only added.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.