Laboratory Tests for Heart Transplant Rejection

Policy Number: 2.01.68  
Last Review: 6/2017  
Next Review: 6/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for the laboratory tests defined below for heart transplant rejection. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
The measurement of volatile organic compounds with the Heartsbreath test to assist in the detection of moderate grade 2R/3 heart transplant rejection is considered investigational.

Considerations
The FDA has indicated that the Heartsbreath test is only 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 and who have had endomyocardial biopsy within the previous month.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
- With heart transplant | Interventions of interest are:  
- Measurement of volatile organic compounds to assess allograft rejection | Comparators of interest are:  
- Routine endomyocardial biopsy | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
- Morbid events  
- Hospitalizations |

| Individuals:  
- With heart transplant | Interventions of interest are:  
- Gene expression profiling to assess allograft rejection | Comparators of interest are:  
- Routine endomyocardial biopsy | Relevant outcomes include:  
- Overall survival  
- Test accuracy  
- Test validity  
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- Hospitalizations |
Several commercially available laboratory tests assess heart transplant rejection, including the Heartsbreath test, which measures breath markers of oxidative stress, and the AlloMap test, which uses gene expression profiling 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.

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 (ie, 20, 30, or 34) for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (ie, 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 posttransplant and 4.3% for patients more than 6 months posttransplant. 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 posttransplant and a small pilot RCT assessing patients starting at 55 days posttransplant. 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 (eg, 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 posttransplant, 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.
Background
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.(1) 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 6 months, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a life-long 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 posttransplant. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following 6 months, and several times (monthly to quarterly) between 6 months and 1 year posttransplant. Surveillance biopsies may also be performed after the first postoperative year (eg, 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, a noninvasive test that measures breath markers of oxidative stress, has been developed to assist in the detection of heart 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, 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 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.(2) All AlloMap testing is performed at the CareDx reference laboratory in Brisbane, California.

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.(3,4)

**Regulatory Status**
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.

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**Rationale**
This evidence review was originally created in November 2004 and has been updated regularly with searches of the MEDLINE database. 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**

Approval of the Heartsbreath test by the U.S. Food and Drug Administration (FDA) 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. The HARDBALL study was a 3-year, multicenter study of 1061 breath samples in 539 heart transplant patients. Before scheduled endomyocardial biopsy, patient breath was analyzed by gas chromatography and mass spectroscopy for volatile organic compounds. The amount of C4 to C20 alkanes and monomethylalkanes was used to derive the marker for rejection, known as the breath methylated alkane contour (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 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 make up the BMAC. The authors also reported finding that in identifying grade 3 rejection, the negative predictive value (NPV) 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 GEP using the AlloMap test. 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 8 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 of transplant rejection, from which 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 (GEP) 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 were 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 posttransplant, 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 posttransplant, 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 posttransplant, 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 posttransplant and 6 (10.2%) of 59 for patients more than 6 months posttransplant.

Section Summary: Clinical Validity
The 2 studies (CARGO, CARGO II) examining the diagnostic performance of GEP using the AlloMap test for detecting moderate/severe rejection are flawed by lack of a consistent threshold (ie, 20, 30, or 34) for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (ie, 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 posttransplant and 4.3% for patients more than 6 months posttransplant.

Clinical Utility
In 2010, results of the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study were published.(9,10) This was an industry-sponsored nonblinded 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 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%. To increase enrollment, the study protocol was later amended to include patients who had undergone transplantation between 6 months and 1 year earlier; this subgroup 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 an LVEF decrease of at least 25% compared with 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 varied 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: (1) the first occurrence of rejection with hemodynamic compromise; (2) graft dysfunction due to other causes; (3) death; or (4) retransplantation. Use of the AlloMap test was considered noninferior to the biopsy strategy if the 1-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 per year in the biopsy group, taken from published observational studies, and allowing for an event rate of up to 10% per year 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. Death from all causes, a secondary outcome, 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 follow-up, there were 34 treated episodes of graft rejection in the AlloMap group. Only 6 (18%) of the 34 patients with graft rejection presented solely with elevated AlloMap scores. Twenty (59%) patients presented with clinical signs/symptoms and/or graft dysfunction on echocardiogram, and 7 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 1249 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 12-Item Short Form Health Survey (SF-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 6 of the 34 treated episodes of graft rejection detected during follow-up in the AlloMap group were initially identified solely due to an elevated gene-profiling score. Since 22 episodes of asymptomatic rejection were detected in the biopsy group, the AlloMap test does not appear to be a sensitive test, possibly missing more than half of the episodes of asymptomatic rejection. Because 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 to 12 months posttransplant.
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.(11) 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 any of the following: 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 a GEP-directed strategy with an endomyocardial biopsy-directed strategy for detecting rejection, which found that the GEP-directed strategy was noninferior. However, given the high proportion of rejection episodes in the GEP-directed strategy group detected by clinical signs/symptoms, the evidence is insufficient to determine that health outcomes are improved because of the uncertain incremental benefit of GEP. In addition, a minority of included subjects were in the first year posttransplant. Results from a pilot RCT suggests that GEP may have a role in evaluating for heart transplant rejection beginning at 55 days posttransplant, but the study was insufficiently powered to allow firm conclusions about the noninferiority of early GEP use.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Active Trials**

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<tr>
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<td>Utility of Donor-Derived Cell-free DNA in</td>
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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.

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SUPPLEMENTAL INFORMATION

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input
In response to requests, input was received from 7 academic medical centers and 1 specialty society while this policy was under review in December 2011. The input was mixed on the question of whether AlloMap should be investigational. Four reviewers agreed with the investigational status, 1 disagreed, and 3 indicated it was a split decision/other. The reviewers were generally in agreement that the sensitivity and specificity has not yet been adequately defined for AlloMap and that the negative predictive value was not sufficiently high to preclude the need for biopsy. There was mixed input about the need for surveillance cardiac biopsies to be performed in the absence of clinical signs and/or symptoms of rejection.

2008 Input
In response to requests, input was received from 2 academic medical centers and 2 physician specialty societies while this policy was under review for November 2008. Three reviewers agreed that these approaches for monitoring heart transplant rejection are considered investigational. The American College of Cardiology (ACC) disagreed with the policy, stating that ACC considers the available laboratory tests to have good potential to diagnose heart transplant rejection and reduce the frequency of invasive biopsies performed on heart transplant patients, although questions remain on their role in clinical practice.

Practice Guidelines and Position Statements
In 2010, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients.(12) The guidelines included the following recommendations:

- “The standard of care for adult HT [heart transplant] recipients is to perform periodic EMB [endomyocardial biopsy] during the first 6 to 12 post-operative months for surveillance of HT rejection.” (class IIa, level of evidence: C)
- After the first post-operative year, EMB surveillance for an extended period of time (eg, every 4–6 months) is recommended in HT patients at higher risk for late acute rejection....” (class IIa, level of evidence: C)
- “Gene Expression Profiling (AlloMap) can be used to rule out the presence of ACR [acute heart rejection] of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT.” (class IIa, level of evidence: B)
U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
In December 2008, the Centers for Medicare and Medicaid Services (CMS) issued a noncoverage decision for the Heartsbreath Test. CMS has determined that the evidence does not adequately define the technical characteristics of the test nor demonstrate that Heartsbreath testing to predict heart transplant rejection improves health outcomes in Medicare beneficiaries.

For AlloMap, there is no National Coverage Determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, and Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare. In 2012, Palmetto conducted a technical assessment and determined that AlloMap meets Medicare’s reasonable and necessary criteria.

References:


**Billing Coding/Physician Documentation Information**

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**ICD-10 Codes**

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**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- 6/1/07 New policy; considered investigational.
- 6/1/08 No policy statement changes.
- 6/1/09 No policy statement changes.
- 6/1/10 No policy statement changes.
- 6/1/11 No policy statement changes.
- 12/1/11 Removed reference to AlloMap from policy.
- 6/1/12 No policy statement changes.
- 6/1/13 No policy statement changes.
- 6/1/14 No policy statement changes.
- 6/1/15 No policy statement changes.
- 6/1/16 No policy statement changes.
- 6/1/17 In first policy statement, “grade 3” changed to “grade 2R/grade 3” due to updated ISHLT rejection grades and brand name of test removed; intent of statements unchanged.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.