2.01.68 Laboratory Tests for Heart Transplant Rejection

Policy Statement

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection is considered investigational.

The use of peripheral blood gene expression profile tests in the management of patients after heart transplantation is considered investigational, including but not limited to:

- Heart transplant graft dysfunction
- The detection of acute heart transplant rejection

Policy Guidelines

The U.S. Food and Drug Administration (FDA) has indicated that the Heartsbreath™ (Menssana Research, Newark, NJ) test is only for use as an aid in the diagnosis of grade 3 (now known as grade 2R) heart transplant rejection in patients who have received heart transplants within the preceding year and who have had endomyocardial biopsy within the previous month.

Coding

There is a CPT category III code for the Heartsbreath™ test:

- 0085T: Breath test for heart transplant rejection

There is a specific CPT code for AlloMap®:

- 81595: Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score

Effective July 1, 2018, the following CPT code is specific to the myTAI HEART™ test:

- 0055U: Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma

Description

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. These tests create a score based on the expression of a variety of immunomodulatory genes and are proposed as an alternative or as an adjunct to invasive endomyocardial biopsy.

Related Policies

- Heart Transplant
- Heart/Lung Transplant
- ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.
Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

In February 2004, the Heartsbreath™ test (Menssana Research) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through a humanitarian device exemption 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) 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 who 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.

**Rationale**

**Background**

**Heart Transplant Rejection**

Most cardiac transplant recipients experience at least a single 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. The revised (R) categories are listed in Table 1.

<table>
<thead>
<tr>
<th>New Grade</th>
<th>Definition</th>
<th>Old Grade</th>
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<tbody>
<tr>
<td>0R</td>
<td>No rejection</td>
<td></td>
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<tr>
<td>1R</td>
<td>Mild rejection</td>
<td>1A, 1B, and 2</td>
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<td>Moderate rejection</td>
<td>3A</td>
</tr>
<tr>
<td>3R</td>
<td>Severe rejection</td>
<td>3B and 4</td>
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</table>

**Surveillance**

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 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 6 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, 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 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 polymerase chain reaction–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, California.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most 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.

**Literature Review**

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (i.e., demonstration that the diagnostic information can be used to improve patient outcomes). The 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. The breath methylated alkane contour 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.¹

The authors of the HARDBALL study reported that the abundance of breath markers that measured oxidative stress were found to be 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 that measure oxidative stress were found to be reduced—most likely due to accelerated catabolism of alkanes and methylalkanes that make up the breath methylated alkane contour. 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% vs 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 evaluating the 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 gene expression profiling (GEP) using the AlloMap test.⁶ The Assessment concluded that the evidence was 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.

**Technical Reliability**

No studies on technical reliability 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.⁷ 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 polymerase chain reaction 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.⁷ 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 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 2016.⁸ 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 test for detecting moderate or severe rejection are flawed by lack of a consistent threshold (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 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, nonblinded, noninferiority randomized controlled trial (RCT) that compared outcomes in 602 patients managed with the AlloMap test (n=297) or with routine endomyocardial biopsies (n=305). The study included adults from 13 centers who underwent cardiac transplantation between 1 and 5 years prior to participating in the study, were clinically stable, and had a left ventricular rejection fraction 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 prior to participating in the study; 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 a left ventricular rejection fraction 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 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 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 GPS 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 post-transplant.

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 post-transplant.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 post-transplant. The threshold for a positive AlloMap test was set at 30 for patients 2 to 6 months post-transplant and 34 for patients after 6 months post-transplant, 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 post-transplant (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, one was detected after an elevated routine AlloMap test, while two 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 or 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; it 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 subjects assessed were in the first year post transplant. Results from a pilot RCT suggests that GEP may have a role in evaluating for heart transplant rejection beginning at 55 days post-transplant, but the trial was insufficiently powered to permit firm conclusions about the noninferiority of early GEP use.

Summary of Evidence
For individuals who have a heart transplant who receive measurement of volatile organic compounds to assess allograft rejection, the evidence includes a 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 (now grade 2R) rejection, the negative predictive value 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 (5.6%) in assessing grade 3 rejection than biopsy (specificity, 97% positive predictive value, 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 a heart transplant who receive GEP to assess allograft rejection, the evidence includes 2 diagnostic accuracy studies and several randomized controlled trials 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 lacked a consistent threshold for defining a positive GEP test (i.e., 20, 30, or 34) and reported a low number of positive cases. In the available studies, although the negative predictive values were relatively high (i.e., at least 88%), the performance characteristics were only calculated based on 10 or fewer cases of rejection; therefore, performance data may be imprecise. Moreover, the positive predictive value 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 randomized control trial 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); further, the IMAGE study failed to provide evidence that GEP offers incremental benefit over biopsy performed on the basis of clinical exam or echocardiography. Patients at the highest risk of transplant rejection are patients within 1 year of the transplant, and for that subset there remains 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.
Supplemental Information

Clinical Input 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.

2012 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 7 academic medical centers and 1 specialty society in 2012. Input was mixed on the question of whether AlloMap should be investigational. Four reviewers agreed with the investigational status, one disagreed, and three indicated it was a split decision/other. 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 from Blue Cross Blue Shield Association, input was received from 2 academic medical centers and 2 physician specialty societies in 2008. Three reviewers agreed that these approaches for monitoring heart transplant rejection are considered investigational. The American College of Cardiology disagreed with the policy, stating that the College 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 as to 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 (see Table 2).

Table 2. Guidelines for Postoperative Care of Heart Transplant Recipients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>&quot;The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 post-operative months for surveillance of HT rejection.&quot;</td>
<td>IIA</td>
<td>C</td>
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<td>&quot;Gene Expression Profiling (AlloMap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT.&quot;</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

ACR: acute heart rejection; COR: class of recommendation; EMB: endomyocardial biopsy; HT: heart transplant; LOE: level of evidence.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

In 2008, the Centers for Medicare & Medicaid Services issued a noncoverage decision for the Heartsbreath Test.13 The Centers determined that the evidence did not adequately define the technical characteristics of the test; nor did it demonstrate that Heartsbreath testing could predict heart transplant rejection, and therefore the test did not improve health outcomes in Medicare beneficiaries.

For AlloMap, there is no national coverage determination. In the absence of a national coverage determination, 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 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Active Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Ongoing and Unpublished Clinical Trials</td>
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<tr>
<td>NCT01833195a</td>
<td>Outcomes AlloMap Registry: the Long-term Management and Outcomes of Heart Transplant Recipients With AlloMap Testing (OAR)</td>
<td>2000</td>
<td>Dec 2018</td>
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<td>NCT02178943a</td>
<td>Utility of Donor-Derived Cell-free DNA in Association With Gene-Expression Profiling (AlloMap®) in Heart Transplant Recipients (D-OAR)</td>
<td>100</td>
<td>Dec 2018</td>
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</table>

NCT: National Clinical Trial.

a Denotes industry-sponsored or cosponsored trial.

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

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<th>Type</th>
<th>Code</th>
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<td>Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma <em>(Code effective 7/1/2018)</em></td>
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<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
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<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</td>
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<td>HCPCS</td>
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**ICD-10 Procedure**

None

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<thead>
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<td>04/05/2007</td>
<td>BCBSA Medical Policy adoption</td>
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<td>03/11/2008</td>
<td>Update CPT code</td>
<td>Administrative Review</td>
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<td>07/01/2011</td>
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<tr>
<td>12/15/2014</td>
<td>Policy title change from Heart Transplant Rejections Laboratory Tests Policy revision with position change effective 2/15/2015</td>
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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.