Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company considers AlloMap™‡ molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the measurement of volatile organic compounds with the Heartsbreath™ test to assist in the detection of grade 2R (formerly grade 3) heart transplant rejection to be investigational.*

Based on review of available data, the Company considers the use of peripheral blood measurement of donor-derived cell-free DNA with the AlloSure test in the management of patients after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, to be investigational.*

Policy Guidelines

The U.S. Food and Drug Administration has indicated that the Heartsbreath (Menssana Research) test is only for use as an aid in the diagnosis of grade 3 (now known as grade 2R) heart transplant
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

rejection in patients who have received heart transplants within the preceding year and who have had endomyocardial biopsy within the previous month.

Background/Overview

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 expression of thousands of genes, including those with functions 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 California.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. They include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most have had low 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.
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

Renal Transplant Rejection
Donor-Derived Cell-Free DNA Testing
cfDNA, released by damaged cells, is normally present in healthy individuals. In patients who have received transplants, dd-cfDNA may be also present. It is proposed that allograft rejection, which is associated with damage to transplanted cells, may result in an increase in dd-cfDNA. AlloSure is a commercially available, next-generation sequencing assay that quantifies the fraction of dd-cfDNA in renal transplant recipients relative to total cfDNA by measuring 266 single nucleotide variants. Separate genotyping of the donor or recipient is not required but patients who receive a kidney transplant from a monozygotic (identical) twin are not eligible for this test. The fraction of dd-cfDNA relative to total cfDNA present in the peripheral blood sample is cited in the report. All AlloSure testing is performed at the CareDx reference laboratory.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
In 2004, the Heartsbreath test (Menssana Research) was cleared for marketing by the U.S. Food and Drug Administration through a humanitarian device exemption for use as an aid in diagnosing grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The device is intended 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 2008, AlloMap Molecular Expression Testing (CareDx, formerly XDx) was cleared for marketing by the Food and Drug Administration through the 510(k) process. The Food and Drug Administration 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 and a low probability of moderate-to-severe transplant rejection. It is intended for patients at least 15 years old who are at least 2 months post transplant.

Rationale/Source
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. Renal transplant rejection may be assessed by the AlloSure test, which
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy #     00148
Original Effective Date:    01/31/2005
Current Effective Date: 12/11/2019

measures the donor-derived cell-free DNA in peripheral blood and is proposed as an alternative or as an adjunct to invasive renal biopsy.

For individuals who have a heart transplant who receive a measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test 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 a lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than a 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 gene expression profiling (GEP) to assess cardiac allograft rejection, the evidence includes two diagnostic accuracy studies and several randomized controlled trials evaluating clinical utility. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The 2 studies, Cardiac Allograft Rejection Gene Expression Observation (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 (ie, 20, 30, or 34) and reported a low number of positive cases. In the available studies, although the negative predictive values were relatively high (ie, 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 two to six months post transplant and 4.3% for patients more than six months 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 Invasive Monitoring Attenuation through Gene Expression (IMAGE) study. In addition, the IMAGE study had several methodologic limitations (eg, 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 one year of the transplant, and, for that subset, there remains insufficient data on which to evaluate
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

the clinical utility of GEP. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a renal transplant and clinical suspicion of allograft rejection who receive testing of donor-derived cell-free DNA to assess renal allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The study examined the diagnostic performance of donor-derived cell-free DNA for detecting moderate-to-severe rejection; the negative predictive value was moderately high (84%), and performance characteristics were calculated on 27 cases of active transplant rejection. The threshold indicating a positive test was not prespecified. 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, input was received from 7 academic medical centers and 1 specialty society while this policy was under review in 2012. Input was mixed on whether AlloMap should be investigational. Four reviewers agreed with the investigational status, one disagreed, and three indicated it was a split decision/other. Reviewers generally agreed that the sensitivity and specificity have 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 in 2008. Three reviewers agreed that these approaches for monitoring heart transplant rejection are considered investigational. The American
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

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 remained as to their role in clinical practice.

Practice Guidelines and Position Statements

International Society of Heart and Lung Transplantation
The International Society of Heart and Lung Transplantation (2010) issued guidelines for the care of heart transplant recipients. The guidelines included the following recommendations (see Table 1).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 postoperative months for surveillance of HT rejection.”</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>“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….”</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>“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.”</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.
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

Kidney Disease Improving Global Outcomes
The Kidney Disease Improving Global Outcomes (2009) issued guidelines for the care of kidney transplant recipients. The guidelines included the following recommendations (see Table 2).

Table 2. Guidelines for Biopsy in Renal Transplant Recipients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine.”</td>
<td>Level 1</td>
<td>C</td>
</tr>
<tr>
<td>“We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection.”</td>
<td>Level 2</td>
<td>D</td>
</tr>
<tr>
<td>“We suggest kidney allograft biopsy every 7-10 days during delayed function.”</td>
<td>Level 2</td>
<td>C</td>
</tr>
<tr>
<td>“We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation.”</td>
<td>Level 2</td>
<td>D</td>
</tr>
<tr>
<td>“We suggest kidney allograft biopsy when there is new onset of proteinuria.”</td>
<td>Level 2</td>
<td>C</td>
</tr>
<tr>
<td>“We suggest kidney allograft biopsy when there is unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours.”</td>
<td>Level 2</td>
<td>C</td>
</tr>
</tbody>
</table>

LOE: level of evidence; SOR: strength of recommendation.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

Medicare National Coverage
The Centers for Medicare & Medicaid Services (2008) issued a noncoverage decision for the Heartsbreath test. 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 would 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 (2012) conducted a technical assessment and determined that AlloMap met Medicare’s reasonable and necessary criteria.

For AlloSure, 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 and Noridian have local coverage determinations on AlloSure.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and 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>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
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</table>
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

<table>
<thead>
<tr>
<th>NCT02178943(^a)</th>
<th>Utility of Donor-Derived Cell-free DNA in Association With Gene-Expression Profiling (AlloMap(^\circ)) in Heart Transplant Recipients (D-OAR)</th>
<th>100</th>
<th>Feb 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03326076(^a)</td>
<td>Evaluation of Patient Outcomes From the Kidney Allograft Outcomes AlloSure Registry</td>
<td>1000</td>
<td>Dec 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.

References
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

8. Blue Cross Blue Shield Technology Evaluation Center (TEC). Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection. TEC Assessment Program. 2011;26(8).
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148  
Original Effective Date: 01/31/2005  
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Policy History

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<thead>
<tr>
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<tbody>
<tr>
<td>01/31/2005</td>
<td>12/11/2019</td>
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</table>

12/07/2004  Medical Director review
12/14/2004  Medical Policy Committee review
01/31/2005  Managed Care Advisory Council approval
07/07/2006  Format revision, including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
01/10/2007  Medical Director review
01/17/2007  Medical Policy Committee approval. New policy statement added regarding evaluation of genetic expression in the peripheral blood.
01/07/2009  Medical Director review
01/14/2009  Medical Policy Committee approval. No change to coverage.
01/07/2010  Medical Policy Committee approval
01/20/2010  Medical Policy Committee Implementation approval. No change to coverage.
01/06/2011  Medical Policy Committee approval
01/19/2011  Medical Policy Committee Implementation approval. No change to coverage.
03/01/2012  Medical Policy Committee review
03/21/2012  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013  Medical Policy Committee review

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Page 11 of 15
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy #  00148
Original Effective Date:  01/31/2005
Current Effective Date:  12/11/2019

05/22/2013  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014  Medical Policy Committee review
05/21/2014  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014  Medical Policy Committee review
11/21/2014  Medical Policy Implementation Committee approval. Added “Based on review of available data, the Company considers AlloMap molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage.” Used to be considered investigational.
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015  Medical Policy Committee review
11/16/2015  Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016  Medical Policy Committee review
12/21/2016  Medical Policy Implementation Committee approval. Added grade 2R category to policy statement.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017  Medical Policy Committee review
12/20/2017  Medical Policy Implementation Committee approval. No change to coverage.
12/06/2018  Medical Policy Committee review
12/19/2018  Medical Policy Implementation Committee approval. Policy statement added that “The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, is considered investigational.” Title expanded to include kidney transplant rejection.
12/05/2019  Medical Policy Committee review
12/11/2019  Medical Policy Implementation Committee approval. No change to coverage.
02/10/2020  Coding update

Next Scheduled Review Date:  12/20/2019
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy #  00148  
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tr>
<td>CPT</td>
<td>0055U, 0085T, 81479, 81595, 86849</td>
</tr>
<tr>
<td></td>
<td>Code added eff 7/1/19: 0087U, 0088U</td>
</tr>
<tr>
<td></td>
<td>Code added eff 10/1/19: 0118U</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

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Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.
Laboratory Tests for Heart and Kidney Transplant Rejection

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2019

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