Laboratory Tests for Heart and Kidney Transplant Rejection

Policy Number: 2.01.68   Last Review: 6/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for the laboratory tests defined below for heart and kidney 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.

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.

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>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With heart transplant</td>
<td>• Measurement of volatile organic compounds to assess cardiac allograft rejection</td>
<td>• Routine endomyocardial biopsy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Test validity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hospitalizations</td>
</tr>
</tbody>
</table>
Several commercially available laboratory tests assess heart transplant rejection, including the Heartsbreath test, which measures breath markers of oxidative stress. 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 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 measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. 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 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. 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.

**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 1. Revised Grading Schema for Cardiac Allograft Rejection

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

**Renal Transplant Rejection**
Allograft dysfunction is typically asymptomatic and has a broad differential, including graft rejection. Diagnosis and rapid treatment are recommended to preserve graft function and prevent loss of the transplanted organ. For a primary kidney transplant, graft survival at 1 year is 94.7%; at 5 years, graft survival is 78.6%.5

**Surveillance**
Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis.6 Allograft dysfunction may also be demonstrated by a drop in urine output or, rarely, as pain over the transplant site. With clinical suspicion of allograft dysfunction, additional noninvasive workup including ultrasonography or radionuclide imaging may be used. A renal biopsy allows a definitive assessment of graft dysfunction and is typically a percutaneous procedure performed with ultrasonography or computed tomography guidance. Biopsy of a transplanted kidney is associated with fewer complications than biopsy of a native kidney because the allograft is typically transplanted more superficially than a native kidney. Renal biopsy is a low-risk invasive procedure that may result in bleeding complications; loss of a renal transplant, as a complication of renal biopsy, is rare.7

Kidney biopsies allow for diagnosis of acute and chronic graft rejection, which may be graded using the Banff Classification.8,9 Pathologic assessment of biopsies demonstrating acute rejection allows clinicians to further distinguish between acute cellular rejection and antibody-mediated rejection, which are treated differently.

**Donor-Derived Cell-Free DNA**
Cell-free DNA (cfDNA), released by damaged cells, is normally present in healthy individuals.10 In patients who have received transplants, donor-derived cfDNA (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.
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 FDA through the 510(k) process. 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 posttransplant.

Rationale
This evidence review was created in November 2004 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through August 22, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Measurement of Volatile Organic Compounds for heart transplant

Clinical Context and Test Purpose
The purpose of measuring volatile organic compounds in patients with a heart transplant is to assess for heart allograft rejection.

The question addressed in this evidence review is: Does the measurement of volatile organic compounds improve the diagnostic assessment of allograft rejection in heart transplant patients?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest is individuals with a heart transplant.

Interventions
The test being considered measures volatile organic compounds to assess for allograft rejection.

Comparators
The following test is currently being used to diagnose heart allograft rejection: routine endomyocardial biopsy.

Outcomes
The general outcomes of interest are overall survival, test validity, morbid events, and hospitalizations.

Timing
Follow-up over months to years is to monitor for signs of allograft rejection.

Setting
Patients with a heart transplant are actively managed by cardiologists and transplant specialists.

Study Selection Criteria
For the evaluation of clinical validity of measuring volatile organic compounds, studies that met the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

U.S. Food and Drug Administration approval of the Heartsbreath test 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 the 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 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 a lower specificity (62.4\%) and a lower positive predictive value (PPV; 5.6\%) in assessing grade 3 rejection than a 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 by Phillips et al (2004). No subsequent studies evaluating the use of the Heartsbreath test to assess for graft rejection were identified in literature updates.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs assessing the measurement of volatile organic compounds to diagnose cardiac allograft rejection were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Because the clinical validity of measuring volatile organic compounds to assess for cardiac allograft rejection has not been established, a chain of evidence to support clinical utility cannot be constructed.

**Section Summary: Clinically Useful**

The published study found that, for identifying grade 3 (now grade 2R) rejection, the 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 a lower specificity (62.4%) and a lower PPV (5.6%) in assessing grade 3 rejection than a biopsy (specificity, 97%; PPV=45.2%). The breath test was also not evaluated for grade 4 rejection.

**Donor-Derived Cell-Free DNA Testing for Renal Transplant**

**Clinical Context and Test Purpose**

The purpose of donor-derived cell-free DNA (dd-cfDNA) testing in patients with renal transplant and clinical suspicion of allograft rejection is to detect allograft rejection.

The question addressed in this evidence review is: Does testing for dd-cfDNA improve outcomes in renal transplant patients with clinical suspicion of allograft rejection?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is individuals with renal transplants and clinical suspicion of allograft rejection.

**Interventions**

The test being considered is dd-cfDNA testing to assess for renal allograft rejection (ie, AlloSure).

**Comparators**

The following test is currently being used to confirm clinical suspicion of allograft rejection: renal biopsy.

**Outcomes**

The general outcomes of interest are overall survival, test validity, morbid events, and hospitalizations.

**Timing**

Follow-up over months to years is to monitor for signs of allograft rejection.

**Setting**

Patients with a renal transplant are actively managed by nephrologists and transplant specialists.
Study Selection Criteria
For the evaluation of clinical validity of dd-cfDNA testing, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse)

Development of the AlloSure test was conducted in the multicenter prospective study by Bloom et al (2017), which both recruited patients who were less than 3 months after renal transplant (n=245) and recruited renal transplant patients requiring a biopsy for suspicion of graft rejection (n=139). For the primary analysis, active rejection was defined as the combined categories of T cell–mediated rejection, acute/active antibody-mediated rejection, and chronic/active antibody-mediated rejection as defined by the Banff working groups. Only patients undergoing biopsy were considered; further exclusion of biopsies which were not for cause, had an inadequate or incomplete collection of biopsies or corresponding blood samples, or had prior allograft in situ resulted in the main study cohort (N=102 patients, 107 biopsies). Within this population, acute rejection was noted in 27 patients (27 biopsies). After statistical analysis accounting for multiple biopsies from the same patient, the threshold dd-cfDNA fraction corresponding to acute rejection was set to 1.0% or higher. In the main study group, this resulted in a sensitivity of 59% (95% CI, 44% to 74%) and specificity of 85% (95% CI, 79% to 81%) for detecting active rejection vs no rejection. Using the original data set including all biopsies performed for clinical suspicion of rejection, 58 cases of acute rejection were diagnosed in 204 biopsies (170 patients). This PPV was 61% and the NPV 84%. Biopsies performed for surveillance (Nn34 biopsies) were excluded from analysis in this study as only one biopsy for surveillance demonstrated acute rejection. Study limitations included the absence of a validation data set.

Section Summary: Clinically Valid
A discovery phase prospective study using the AlloSure test has been performed in a multicenter setting. Larger studies validating the dd-cfDNA threshold for active rejection are needed to develop conclusions.
**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of the dd-cfDNA (AlloSure) testing to diagnose renal allograft rejection were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of dd-cfDNA (AlloSure) testing to assess for renal allograft rejection has not been established, a chain of evidence support clinical utility cannot be constructed.

**Section Summary: Clinically Useful**

At present, no studies evaluating the clinical utility for the dd-cfDNA (AlloSure) testing were identified.

**Summary of Evidence**

For individuals who have a heart transplant who receive measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. 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 GEP to assess cardiac allograft rejection, the evidence includes 2 diagnostic accuracy studies and several randomized controlled trials evaluating clinical utility. Relevant outcomes are overall survival, test 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 (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 2 to 6 months posttransplant and 4.3% for patients more than 6 months 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); 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.

For individuals with a renal transplant and clinical suspicion of allograft rejection who receive testing of dd-cfDNA to assess renal allograft rejection, the evidence includes a diagnostic accuracy study. Relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The study examined the diagnostic performance of dd-cfDNA 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 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

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 3).

<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.

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 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 unpublished trials that might influence this review are listed in Table 4.

### 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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<tr>
<td>NCT0332607 6</td>
<td>Evaluation of Patient Outcomes From the Kidney Allograft Outcomes AlloSure Registry (KOAR)</td>
<td>1000</td>
<td>Dec 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.

References


Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
</tr>
<tr>
<td>0055U</td>
<td>Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target</td>
</tr>
<tr>
<td></td>
<td>sequences (94 single nucleotide polymorphism targets and two control targets), plasma</td>
</tr>
<tr>
<td>0087U</td>
<td>Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score (New Code as of 7/1/2019)</td>
</tr>
<tr>
<td>0088U</td>
<td>Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection (New Code as of 7/1/2019)</td>
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</table>

ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T86.20-</td>
<td>Complications of heart transplant code range</td>
</tr>
<tr>
<td>T86.298</td>
<td></td>
</tr>
<tr>
<td>Z48.21</td>
<td>Encounter for aftercare following heart transplant</td>
</tr>
<tr>
<td>Z94.1</td>
<td>Heart transplant status</td>
</tr>
</tbody>
</table>

Additional Policy Key Words

Allosure
Heartsbreath

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.
6/1/18  No policy statement changes.
1/1/19  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.
6/1/19  No policy statement changes.

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