Laboratory Tests for Heart and Kidney Transplant Rejection

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. 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.

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
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.

OBJECTIVE

The objective of this evidence review is to determine whether measurement of volatile organic compounds or use of gene expression profiling improve detection of allograft rejection in heart transplant patients, and to determine whether testing of the percentage of donor-derived cell-free DNA improves detection of allograft rejection in renal transplant patients, thus improving net health outcomes.

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, including but not limited to the detection of acute heart transplant rejection or heart transplant graft dysfunction, 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.

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

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
FDA REGULATORY STATUS

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.

cfDNA, released by damaged cells, is normally present in healthy individuals. In patients who have received transplants, dd-cfDNA may also be 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.

RATIONALITY

Summary of Evidence

For individuals with 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 (OS), test validity, morbid events, and hospitalizations. The published study found that, for identifying grade 3 (now grade 2R) rejection, the negative predictive value (NPV) of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test (78.6%) was better than that for biopsy (42.4%). However, the breath test had 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%). 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 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 (RCTs) evaluating clinical utility. The relevant outcomes are OS, 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 NPVs 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 PPV 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 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 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 (dd-cfDNA) to assess renal allograft rejection, the evidence includes a diagnostic accuracy study. The relevant outcomes are overall survival (OS), test validity, morbid events, and hospitalizations. The study examined the diagnostic performance of dd-cfDNA for detecting...
moderate-to-severe rejection; the NPV 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

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 1. 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 postoperative months for surveillance of HT rejection.&quot;</td>
<td>IIa</td>
<td>C</td>
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<tr>
<td>&quot;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....&quot;</td>
<td>IIa</td>
<td>C</td>
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<tr>
<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.

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>
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<td>&quot;We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine.&quot;</td>
<td>Level 1</td>
<td>C</td>
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<tr>
<td>&quot;We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection.&quot;</td>
<td>Level 2</td>
<td>D</td>
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</table>
"We suggest kidney allograft biopsy every 7-10 days during delayed function." | Level 2 | C

"We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation." | Level 2 | D

"We suggest kidney allograft biopsy when there is new onset of proteinuria." | Level 2 | C

"We suggest kidney allograft biopsy when there is unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours." | Level 2 | C

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 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.

### REFERENCES


7. 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).


**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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<td>June 2012</td>
<td>New policy</td>
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<tr>
<td>June 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 5, 2015. References 2-3 and 12 added. Policy statements unchanged.</td>
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<tr>
<td>June 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 4, 2014; reference 9 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review, References removed and renumbered. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 28, 2017; no references added; reference 2 updated. 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. Policy statement corrected from “not medically necessary” to “investigational”.</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 22, 2018; references 5-9, 18, 20, and 22 added. 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.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 5, 2019; no references added. Policy statements unchanged.</td>
</tr>
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