This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended. The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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

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.

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 gene expression profiling (GEP) to assess allograft rejection, the evidence includes two diagnostic accuracy studies and several randomized controlled trials (RCTs) evaluating clinical utility. Relevant outcomes are overall survival, test accuracy and validity, morbid events, and hospitalizations. The two 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 two to six months posttransplant and 4.3% for patients more than six months posttransplant. The clinical utility of GEP compared with routine endomyocardial biopsies has been evaluated in two RCTs, the IMAGE study assessing patients more than six months posttransplant and a small pilot RCT assessing patients starting at 55 days posttransplant. The threshold indicating a positive test that seems to be currently accepted (a score of 34) was not prespecified; rather it evolved partway through the data collection period in the IMAGE study. In addition, the IMAGE study had several methodologic limitations (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 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.

POLICY

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.

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.

MEDICARE ADVANTAGE

AlloMap™ may be considered medically necessary for the FDA approved indication to aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment.

Any other uses of Allomap are considered investigational.

The Heartsbreath™ test is considered investigational.
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.1 The revised (R) categories are listed in Table 1.

<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 six 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 six 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 six months, and several times (monthly to quarterly) between six months and one 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 one 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 zero 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.

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. 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 two months posttransplant.

RELATED PROTOCOLS

Heart Transplant
Heart/Lung Transplant

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.
14. Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160), Revision Effective Date for services performed on or after 01/01/2018.