Protocol

Laboratory Tests for Heart and Kidney Transplant Rejection

(20168)

Medical Benefit		**Effective Date**: 02/01/20	**Next Review Date**: 11/20
Preauthorization	No	**Review Dates**: 05/13, 05/14, 05/15, 05/16, 05/17, 05/18, 11/18, 07/19, 11/19	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With heart transplant	Interventions of interest are: • Measurement of volatile organic compounds to assess cardiac allograft rejection	Comparators of interest are: • Routine endomyocardial biopsy	Relevant outcomes include: • Overall survival • Test validity • Morbid events • Hospitalizations
Individuals: • With heart transplant	Interventions of interest are: • Gene expression profiling to assess cardiac allograft rejection	Comparators of interest are: • Routine endomyocardial biopsy	Relevant outcomes include: • Overall survival • Test validity • Morbid events • Hospitalizations
Individuals: • With renal transplant and clinical suspicion of allograft rejection	Interventions of interest are: • Testing donor-derived cell-free DNA in blood to assess allograft rejection	Comparators of interest are: • Renal biopsy	Relevant outcomes include: • Overall survival • Test validity • Morbid events • Hospitalizations

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.

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 gene expression profiling (GEP) to assess cardiac allograft rejection, the evidence includes two diagnostic accuracy studies and several randomized controlled trials evaluating clinical utility. Relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The two 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 (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 ten 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 (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.

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.

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**.

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 (FDA) 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.

MEDICARE ADVANTAGE

AlloMap™ may be considered **medically necessary** for heart transplant patients to guide therapeutic decision-making.

Any other uses of Allomap are considered **not medically necessary.**

The Heartsbreath™ test is considered **not medically necessary.**

The AlloSure™ assay test is considered **medically necessary** only when the following clinical conditions are met:

- Renal allograft recipients >18 years
- Physician-assessed pretest need to further assess patient for the probability of active renal allograft rejection
- At least two weeks post-transplant.

BACKGROUND

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.[1] 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.[2,3]

RENAL TRANSPLANT REJECTION

Donor-Derived Cell-Free DNA

Cell-free DNA (cfDNA), released by damaged cells, is normally present in healthy individuals.[4] 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 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 two months post-transplant.

RELATED PROTOCOLS

Heart Transplant

Heart/Lung Transplant

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

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