DRAFT Medical Coverage Policy | Laboratory Tests for Heart and Kidney Transplant Rejection

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OVERVIEW

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.

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products

Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare and Commercial Products

There is no specific CPT code for the AlloSure assay and an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

POLICY STATEMENT

BlueCHiP for Medicare

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection, such as the Heartsbreath test, is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

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, such as myTAIHeart, is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

The use of the peripheral blood gene expression profile test AlloMap for heart transplant rejection is covered.

The AlloSure test to assess the probability of allograft rejection for kidney transplant covered.

The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation, other than AlloSure, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection, such as the Heartsbreath test, is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

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, such as AlloMap and myTAIHeart, is not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation, such as AlloSure, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction, is not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for laboratory tests or not medically necessary/not covered benefits/coverage.

BACKGROUND

HEART TRANSPLANT REJECTION

Most cardiac transplant recipients experience at least a single episode of rejection in the first year after transplantation.

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 (eg, 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, a 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 are 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 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.2 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.

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%.

Surveillance

Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis. 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. Kidney biopsies allow for diagnosis of acute and chronic graft rejection, which may be graded using the Banff Classification. 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. 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 ddcfDNA.

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.

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 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, 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 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 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 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 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.

BlueCHiP for Medicare

AlloMap testing is considered medically necessary for heart transplant patients to guide therapeutic decision-making.

The AlloSure donor-derived cell-free DNA test (CareDx, Inc., Brisbane, CA) is used to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of renal biopsy in such patients at least 2 weeks post-transplant in conjunction with standard clinical assessment.

A significant challenge in the management of kidney transplant patients is the poor sensitivity and specificity of tests or procedures for immune monitoring and graft function. The AlloSure test for donor-derived cell-free DNA (ddcfDNA) detected in the blood of transplant recipients has been developed as a noninvasive marker for diagnosis of graft rejection. The premise for AlloSure is that rejection entails injury, including increased cell death in the allograft, leading to increased dd-cfDNA released into the bloodstream.

CODING

The following CPT codes are not covered for BlueCHiP for Medicare and not medically necessary for Commercial Products.
This code can be used for the Heartsbreath test:
0085T Breath test for heart transplant rejection
This code can be used for the myTAIHeart test:
0055U Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma

The following CPT code is covered for BlueCHiP for Medicare and not medically necessary for Commercial Products.
This code can be used for AlloMap:
81595 Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score

There is no specific CPT code for AlloSure, therefore Unlisted CPT code 81479 should be used.
CPT code 81479 requires prior authorization for BlueCHiP for Medicare and Commercial Products.

RELATED POLICIES

Genetic Testing Services
New Technology
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update,

REFERENCES

1. Centers for Medicare& Medicaid Services. Local Coverage Determination (LCD): MolDX: AlloSure® Donor-Derived Cell-Free DNA Test (L37303)
2. Centers for Medicare& Medicaid Services. National Coverage Determination (NCD) for HEARTSBREATH Test for Heart Transplant Rejection (260.10)
3. Centers for Medicare& Medicaid Services. Local Coverage Article: Category III CPT® Codes-Related to Category III CPT® Codes (L33392) (A56195)
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