Laboratory Tests for Heart and Kidney Transplant Rejection

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 use gene expression profiling (GEP) to generate a score based on the expression of various immunomodulatory genes. These tests are proposed as alternatives to, or adjunct to, endomyocardial biopsy, which is invasive. 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 to, or adjunct to, invasive renal biopsy.

Heart Transplant Rejection
Most cardiac transplant recipients experience at least one 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. Revised (R) categories are as follows:

- Grade 0R: No rejection
- Grade 1R: Mild rejection (previously Grades 1A, 1B and 2)
- Grade 2R: Moderate rejection (previously Grade 3A)
- Grade 3R: Severe rejection (previously Grades 3B and 4)

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 6-12 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 a year post-transplant. Surveillance biopsies may also be performed after the first postoperative year e.g., on a quarterly or semi-annual basis. This practice, although common, has not been demonstrated to improve transplant outcomes. Some centers no longer routinely perform endomyocardial biopsies after a 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 non-invasive tests will assist in determining appropriate patient
Laboratory Tests for Heart and Kidney Transplant Rejection

management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false negative and false positive biopsy reports.

**Noninvasive Heart Transplant Rejection Tests**
The Heartsbreath test, is 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 that 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-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 (PCR) 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 PCR 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 cut-off for a positive test. All AlloMap testing is performed at the CareDx reference laboratory in Brisbane, CA.

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most of these 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.

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

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. Renal biopsy allows 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, as 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 (ACR) and antibody-mediated rejection (AMR), which are treated differently.
Laboratory Tests for Heart and Kidney Transplant Rejection

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 also be present. It has been 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 (NGS) assay which quantifies the fraction of dd-cfDNA in renal transplant recipients, relative to total cfDNA, by measuring 266 single nucleotide variants (SNVs). Separate genotyping of the donor or recipient is not required, but patients who received a kidney transplant from a monozygotic (identical) twin are not eligible for this test. All AlloSure testing is performed in the CareDx reference laboratory.

REGULATORY STATUS
In 2004, the Heartsbreath™ test (Menssana Research) received approval for marketing from the U.S. Food and Drug Administration (FDA) through a humanitarian device exemption. The Heartsbreath test is indicated 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 2008, AlloMap® Molecular Expression Testing (CareDx, formerly XDx) was cleared for marketing by the 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-to-severe transplant rejection. It is intended for patients at least 15 years old who are at least 2 months post-transplant.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Heartsbreath testing for heart transplant rejection detection is considered investigational. BCBSNC does not provide coverage for investigational services.

BCBSNC may provide coverage for AlloMap molecular expression testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Peripheral blood measurement of donor-derived cell-free DNA (i.e., AlloSure) in the management of patients after renal transplantation, including but not limited to the detection of acute transplant rejection or renal transplant graft dysfunction is considered investigational. BCBSNC does not provide coverage for investigational services.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Laboratory Tests for Heart Transplant Rejection is covered
AlloMap molecular expression testing is considered medically necessary as a non-invasive method of determining the risk of rejection in heart transplant recipients between 1 and 5 years post-transplant.
Laboratory Tests for Heart and Kidney Transplant Rejection

When Laboratory Tests for Heart Transplant Rejection is not covered

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection is considered investigational.

AlloMap molecular expression testing, is considered investigational when the criteria above are not met.

Peripheral blood measurement of donor-derived cell-free DNA (i.e., AlloSure) in the management of patients after renal transplantation, including but not limited to the detection of acute transplant rejection or renal transplant graft dysfunction is considered investigational.

Policy Guidelines

Evidence includes 1 diagnostic accuracy study for those who have a heart transplant and are tested with measurement of volatile organic compounds to assess cardiac allograft rejection. 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 (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 lower specificity (62.4%) and a lower positive predictive value (PPV=5.6%) in assessing grade 3 rejection than 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 those who have a heart transplant and are tested with gene expression profiling (GEP) to assess cardiac allograft rejection, evidence includes 2 diagnostic accuracy studies and several randomized controlled trials (RCTs) 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 lack a consistent threshold for defining a positive GEP test (ie, 20, 30, or 34) for determining positivity and a small number of positive cases. In the available studies, although the NPVs were relatively high (ie, at least 88%), the performance characteristics were calculated based on only 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 2 to 6 months posttransplant and 4.3% for patients more than 6 months posttransplant. However, it is concluded that choice of threshold score for the practical use of GEP testing with AlloMap should consider the overall clinical assessment of the individual’s baseline risk for rejection. The clinical utility of GEP compared with routine endomyocardial biopsies has been evaluated in 2 RCTs, the IMAGE study assessing patients more than 6 months posttransplant and a small pilot RCT assessing patients starting at 55 days posttransplant. The purpose of the study was to compare rejection outcomes between those who underwent routine EMB and those who were monitored with AlloMap gene expression profiling test. The primary outcome was the first occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. Results indicated that a strategy of monitoring for rejection that involved gene-expression profiling, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies. During the median follow-up period (19 months), subjects who were monitored with AlloMap and those who underwent routine EMB had similar 2-year cumulative rates of the composite primary outcome. The 2-year rate of death from any cause were also similar in the two groups. Although the limited power of the study did not allow for firm conclusions regarding the utility of AlloMap as a substitute for EMB, the authors concluded that gene expression profiling of peripheral blood specimens may offer a reasonable alternative to routine biopsies, for monitoring cardiac transplant rejection, if it has
Laboratory Tests for Heart and Kidney Transplant Rejection

been at least 6 months since transplantation and the individual is considered at low risk for rejection.

In 2010, the International Society of Heart and Lung Transplantation (ISHLT) issued guidelines for the care of heart transplant recipients which included the following:

- The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy (EMB) during the first 6-12 months after transplant for rejection surveillance;
- After the first year post-transplant, EMB surveillance every 4-6 months is recommended for patients at higher risk of late acute rejection;
- Gene expression profiling using the AlloMap test can be used to rule out acute heart rejection (grade 2 or greater) in appropriate low-risk patients between 6 months and 5 years post-transplant.

The current International Society of Heart and Lung Transplantation (ISHLT) recommendations for the use of AlloMap in limited clinical protocols, and the results of the IMAGE study, support the use of AlloMap to assess risk for rejection in clinically stable heart transplant recipients between 1 and 5 years post-transplant.

The evidence for individual with a renal transplant and clinical suspicion of allograft rejection, who receive testing of donor-derived cell-free DNA to assess renal allograft rejection includes, diagnostic accuracy studies. Relevant outcomes are overall survival, test validity, morbid events, and hospitalizations. The study, which examined the diagnostic performace 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0085T, 81595, 86849, 0055U, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy titled: Breath Testing for Heart Transplant Rejection Detection


Specialty Matched Consultant Advisory Panel - 11/05

Laboratory Tests for Heart and Kidney Transplant Rejection


For Policy renamed: Laboratory Tests for Heart Transplant Rejection


Senior Medical Director review 2/2011


Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection. TEC Assessments 2011.

Specialty Matched Consultant Advisory Panel review 4/2012


Specialty Matched Consultant Advisory Panel review 4/2013


Medical Director review 4/2014
Laboratory Tests for Heart and Kidney Transplant Rejection

Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 4/2016


Medical Director review 5/2016


Specialty Matched Consultant Advisory Panel review 4/2017

Medical Director review 4/2017


Specialty Matched Consultant Advisory Panel review 4/2018

Medical Director review 4/2018

For Policy renamed: Laboratory Tests for Heart and Kidney Transplant Rejection


Medical Director review 10/2018

Policy Implementation/Update Information

For Policy titled: Breath Testing for Heart Transplant Rejection Detection

Laboratory Tests for Heart and Kidney Transplant Rejection

11/17/05  Specialty Matched Consultant Advisory Panel review 11/07/05. No change to policy.

11/19/07  References updated. Specialty Matched Consultant Advisory Panel review meeting

10/29/07  No change to policy statement. (adn)

For Policy renamed: Laboratory Tests for Heart Transplant Rejection

12/7/09  Policy name changed from "Breath Testing for Heart Transplant Rejection Detection" to "Laboratory Tests for Heart Transplant Rejection." Description section revised for clarity. Added the following Policy Statement: BCBSNC does not provide coverage for the evaluation of genetic expression in the peripheral blood to detect acute heart transplant rejection or graft dysfunction. It is considered investigational. Statement in the Not Covered section revised to read: The measurement of volatile organic compounds in breath to assist in the detection of grade 3 heart transplant rejection is considered investigational. Also added the following statement to the Not Covered section: The evaluation of genetic expression in the peripheral blood, including, but not limited to, the detection of acute heart transplant rejection or graft dysfunction is considered investigational. Policy Guidelines updated to include FDA information regarding the Heartsbreath test and rationale for the investigational status of the AlloMap™ test. References updated. Specialty Matched Consultant Advisory Panel review meeting 10/30/09. Approved policy revisions. (adn)

6/22/10  Policy Number(s) removed (amw)

10/26/10  CPT code 86849 added to Billing/Coding section. (mco)

3/1/11  Description section updated. References updated. Reviewed by Senior Medical Director. (mco)


12/30/15  Billing/Coding section updated to include code 81595; effective 1/1/16. (td)


7/1/16  Description section extensively updated. Non-Covered section updated from “grade 3” to “grade 2R/grade 3” due to updated rejection grades and brand name of test removed. Policy Guidelines and references updated. Medical Director review 4/2016. (jd)

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Laboratory Tests for Heart and Kidney Transplant Rejection


6/29/18    Added code 0055U to Billing/Coding section, effective 7/1/18. (jd)

For Policy renamed: Laboratory Tests for Heart and Kidney Transplant Rejection

11/9/18    Policy name changed from “Laboratory Tests for Heart Transplant Rejection” to “Laboratory Tests for Heart and Kidney Transplant Rejection”. Description section revised to include renal transplant rejection and donor-derived cell-free DNA. Added the following Policy Statement: “Peripheral blood measurement of donor-derived cell-free DNA (i.e., AlloSure) in the management of patients after renal transplantation, including but not limited to the detection of acute transplant rejection or renal transplant graft dysfunction is considered investigational. BCBSNC does not provide coverage for investigational services.” Statement in the Not Covered section added as follows: “Peripheral blood measurement of donor-derived cell-free DNA (i.e., AlloSure) in the management of patients after renal transplantation, including but not limited to the detection of acute transplant rejection or renal transplant graft dysfunction is considered investigational.” Policy Guidelines updated to support policy statement. Coding section updated with addition of code 81479. References updated. Medical Director review 10/2018. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.