Laboratory Tests Post Transplant

Policy # 00148
Original Effective Date: 01/31/2005
Current Effective Date: 12/11/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider MMDx Heart and AlloMap™‡ molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for molecular expression testing will be considered when all of the following criteria are met:

- Patient is at least 15 years of age; and
- Between 6 months and 5 years post-transplant; and
- Recipient must have stable heart allograft function (i.e., left ventricular ejection fraction 45% or greater, no evidence of congestive heart failure); and
- Testing is performed in lieu of routinely scheduled endomyocardial biopsies and result will be used to determine the need for subsequent endomyocardial biopsy to clarify rejection status.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers the measurement of volatile organic compounds with the Heartsbreath™‡ test to assist in the detection of grade 2R (formerly grade 3) heart transplant rejection to be **investigational.***

Based on review of available data, the Company considers the use of peripheral blood measurement of donor-derived cell-free DNA (dd-cf DNA) testing for transplant rejection status **investigational***, including but not limited to the following:

- The use of peripheral blood measurement of dd-cf DNA (e.g., AlloSure, Prospera) 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;
- The use of peripheral blood measurement of dd-cfDNA in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection;
- The use of peripheral blood gene expression profile tests in combination with peripheral blood measurement of dd-cf DNA (e.g., HeartCare) 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;
- The use of peripheral blood measurement of dd-cf DNA (e.g., AlloSure, Viracor) in the management of patients after lung transplantation, including but not limited to the detection of acute lung transplant rejection or lung transplant graft dysfunction;

Based on review of available data, the Company considers other tests and uses of AlloMap™‡ molecular expression testing when the above criteria are not met to be **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.

Background/Overview

Heart Failure

Heart failure is a major cause of morbidity and mortality worldwide. The term *heart failure* refers to a complex clinical syndrome that impairs the heart's ability to move blood through the circulatory system. The prevalence of heart failure in the U.S. between 2013 and 2016 was an estimated 6.2 million for Americans ≥20 years old, up from 5.7 million between 2009 and 2012. Heart failure is the leading cause of hospitalization among people older than age 65 years, with direct and indirect costs estimated at $37 billion annually in the U.S. Although survival has improved with treatment advances, absolute mortality rates of heart failure remain near 50% within 5 years of diagnosis.

Physiology

Heart failure can be caused by disorders of the pericardium, myocardium, endocardium, heart valves or great vessels, or metabolic abnormalities. Individuals with heart failure may present with a wide range of left ventricular (LV) anatomy and function. Some have normal LV size and preserved ejection fraction; others have severe LV dilatation and depressed ejection fraction. However, most patients present with key signs and symptoms secondary to congestion in the lungs from impaired LV myocardial function. They include dyspnea, orthopnea, and paroxysmal dyspnea. Other symptoms include weight gain due to fluid retention, fatigue, weakness, and exercise intolerance secondary to diminished cardiac output.

Diagnosis

Initial evaluation of a patient with suspected heart failure is typically based on clinical history, physical examination, and chest radiograph. Because people with heart failure may present with nonspecific signs and symptoms (eg, dyspnea), accurate diagnosis can be challenging. Therefore, noninvasive imaging procedures (eg, echocardiography, radionuclide angiography) are used to quantify pump function of the heart, thus identifying or excluding heart failure in patients with characteristic signs and symptoms. These tests can also be used to assess prognosis by determining the severity of the underlying cardiac dysfunction. However, clinical assessment and noninvasive imaging can be limited in accurately evaluating patients with heart failure because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. Thus, invasive procedures (eg, cardiac angiography, catheterization) are used in select patients with presumed heart failure symptoms to determine the etiology (ie, ischemic vs. nonischemic) and physiologic characteristics of the condition.

Treatment

Patients with heart failure may be treated using a number of interventions. Lifestyle factors such as the restriction of salt and fluid intake, monitoring for increased weight, and structured exercise programs are beneficial components of self-management. A variety of medications are available to treat heart failure. They include diuretics (eg, furosemide, hydrochlorothiazide, spironolactone), angiotensin-converting enzyme inhibitors (eg, captopril, enalapril, lisinopril), angiotensin receptor blockers (eg, losartan, valsartan, candesartan), b-blockers (eg, carvedilol, metoprolol succinate), and vasodilators (eg, hydralazine, isosorbide dinitrate). Numerous device-based therapies are also available. Implantable cardioverter defibrillators reduce mortality in patients with an increased risk of sudden cardiac death. Cardiac resynchronization therapy improves symptoms and reduces mortality for patients who have disordered LV conduction evidenced by a wide QRS complex on electrocardiogram. Ventricular assist devices are indicated for patients with end-stage heart failure who have failed all other therapies and are also used as a bridge to cardiac transplantation in select patients.

Heart Failure Biomarkers

Because of limitations inherent in standard clinical assessments of patients with heart failure, a number of objective disease biomarkers have been investigated to diagnose and assess heart failure patient prognosis, with the additional goal of using biomarkers to guide therapy. They include a number of proteins, peptides, or other small molecules whose production and release into circulation reflect the activation of remodeling and neurohormonal pathways that lead to LV impairment. Examples include B-type natriuretic peptide (BNP), its analogue N-terminal pro B-type natriuretic peptide (NT-proBNP), troponin T and I, renin, angiotensin, arginine vasopressin, C-reactive protein, and norepinephrine.

BNP and NT-proBNP are considered the reference standards for biomarkers in assessing heart failure patients. They have had a substantial impact on the standard of care for diagnosis of heart failure and are included in the recommendations of all major medical societies, including the American College of Cardiology Foundation and American Heart Association, European Society of Cardiology, and the Heart Failure Society of America. Although natriuretic peptide levels are not 100% specific for the clinical diagnosis of heart failure, elevated BNP or NT-proBNP levels in the presence of clinical signs and symptoms reliably identify the presence of structural heart disease due to remodeling and heightened risk for adverse events. Natriuretic peptides also can help in

determining the prognosis of heart failure patients, with elevated blood levels portending a poorer prognosis.

In addition to diagnosing and assessing the prognosis of heart failure patients, blood levels of BNP or NT-proBNP have been proposed as an aid for managing patients diagnosed with chronic heart failure. Levels of either biomarker rise in response to myocardial damage and LV remodeling, whereas they tend to fall as drug therapy ameliorates symptoms of heart failure. Evidence from a large number of randomized controlled trials (RCTs) that have compared BNP- or NT-proBNP-guided therapy with clinically guided adjustment of pharmacologic treatment of patients who had chronic heart failure has been assessed in recent systematic reviews and meta-analyses. However, these analyses have not consistently reported a benefit for BNP-guided management. Savarese et al (2013) published the largest meta-analysis to date–a patient-level meta-analysis that evaluated 2686 patients from 12 RCTs. This meta-analysis showed that NT-proBNP-guided management was associated with significant reductions in all-cause mortality and heart failure-related hospitalization compared with clinically guided treatment. Although BNP-guided management in this meta-analysis was not associated with significant reductions in these parameters, differences in patient numbers and characteristics may explain the discrepancy. Troughton et al (2014) conducted a second patient-level meta-analysis that included 11 RCTs with 2000 patients randomized to natriuretic peptide-guided pharmacologic therapy or usual care. The results showed that, among patients 75 years of age or younger with chronic heart failure, most of whom had impaired left ventricular ejection fraction, natriuretic peptide-guided therapy was associated with significant reductions in all-cause mortality compared with clinically guided therapy. Natriuretic-guided therapy also was associated with significant reductions in hospitalization due to heart failure or cardiovascular disease.

Heart Transplant Rejection

Most cardiac transplant recipients experience at least a single episode of rejection in the first year after transplantation. The International Society for Heart and Lung Transplantation (2005) modified its grading scheme for categorizing cardiac allograft rejection. The revised (R) categories are listed in Table 1.

Table 1. Revised Grading Schema for Cardiac Allograft Rejection

New Grade	Definition	Old Grade
0R	No rejection	

1R	Mild rejection	1A, 1B, and 2
2R	Moderate rejection	3A
3R	Severe rejection	3B and 4

Acute cellular rejection is most likely to occur in the first 6 months after transplantation, 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 post transplant. 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 post transplant. 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 the endomyocardial biopsy is the criterion standard for assessing heart transplant rejection, it is limited by a high degree of interobserver variability in the 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, an 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

HeartCare

Cell-free DNA (cfDNA), released by damaged cells, is normally present in healthy individuals. In patients who have received transplants, donor-derived cell-free DNA (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. HeartCare (CareDx) is a commercially-available test that combines AlloMap gene expression profiling with a next-generation sequencing assay that quantifies the fraction of dd-cfDNA in cardiac transplant recipients relative to total cfDNA. The AlloMap score, AlloMap score variability, and AlloSure % dd-cfDNA are reported.

AlloMap

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 (CareDx) 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. 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, from a deceased donor (accounting for about 70% of kidney donors), graft survival at 1 year is 95%; at 5 years, graft survival is 78%.

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.

Noninvasive Renal Transplant Rejection Tests

Allosure

AlloSure Kidney (CareDx) 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. For patients undergoing surveillance, a routine testing schedule is recommended for longitudinal monitoring.

Prospera
Prospera Kidney (Natera) is a commercially available assay that quantifies the fraction of dd-cfDNA in renal transplant recipients. The manufacturer recommends use of the Prospera test when there is clinical suspicion of active rejection and for regular surveillance of subclinical rejection in renal transplant recipients. In a surveillance scenario, regular testing is recommended at 1, 2, 3, 4, 6, 9 and 12 months after renal transplant or most recent rejection. Thereafter, the test should be repeated quarterly. The proportion of dd-cfDNA relative to total cfDNA is reported, with detection of ≥1% dd-cfDNA indicating increased risk for active rejection. The percent dd-cfDNA change between tests is also reported.

TruGraf
TruGraf offers a gene expression panel intended for kidney transplant patients, based on microarray analysis of peripheral blood. TruGraf proposes that it can identify if a patient is "immune activating" (potentially rejecting) or "immune quiescent" (stable), allowing a clinician to evaluate potential pre-symptomatic kidney damage without use of a biopsy. However, many barriers impede the introduction of these novel biomarkers into clinical practice, including their generalizability and difficulties in identifying patient populations who may benefit from more than standard-of-care surveillance.

Innovative strategies have been developed and several noninvasive monitoring tools have been proposed that use easily accessible biologic fluids such as urine and blood, allowing frequent and sequential assessments of a recipient's immune status. These include functional cell-based assays and the evaluation of molecular expression, at the messenger RNA (mRNA) or protein level, on a wide spectrum of platforms. Molecular technologies, including the molecular microscope diagnostic system (MMDx), have been developed over the past decade as a refinement of the histologic evaluation of the allograft biopsy. The translation and validation of exploratory findings and their implementation into standard clinical practice remain challenging. Dedicated, prospective, interventional trials are required to demonstrate that the use of these biomarkers improves patient or transplant outcomes.

Lung Transplant Rejection
Despite advances in induction and maintenance immunosuppressive regimens, lung transplant recipients have a median overall survival of 6 years, with more than a third of patients receiving treatment for acute rejection in the first year after transplant. Acute cellular rejection, lymphocytic

bronchiolitis, and antibody-mediated rejection are all risk factors for subsequent development of chronic lung allograft dysfunction (CLAD). Pathologic grading of acute cellular rejection is based on the histological assessment of perivascular and interstitial mononuclear cell infiltrates. Antibody-mediated rejection may be clinical (symptomatic or asymptomatic allograft dysfunction) or subclinical (normal allograft function). Key diagnostic criteria established via consensus by the International Society for Heart and Lung Transplantation include the presence of antibodies directed toward donor human leukocyte antigens and characteristic lung histology with or without evidence of complement 4d within the graft. The most common phenotype of CLAD is a persistent obstructive decline in lung function known as bronchiolitis obliterans syndrome (BOS), which is graded based on the degree of decrease in FEV_1. Approximately 50% of patients develop BOS within 5 years post-transplant. Median survival following a diagnosis of BOS is 3-5 years. Acute rejection may present with non-specific physical symptoms or be asymptomatic. However, the role of surveillance bronchoscopy for screening asymptomatic patients for acute rejection is controversial, and performance of surveillance bronchoscopies varies across transplant centers.

Noninvasive Lung Transplant Rejection Tests

AlloSure
AlloSure Lung (CareDx) is a commercially available, NGS assay that quantifies the fraction of dd-cfDNA in lung transplant patients relative to total cfDNA by measuring single nucleotide polymorphisms. The test is intended to provide a direct, noninvasive measure of organ injury in lung transplant patients who are undergoing surveillance. Suggested thresholds for severe injury, injury, and quiescence are 1%, 0.85%, and <0.5%, respectively.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. FDA has cleared multiple biomarker tests for the detection of heart and renal allograft rejection. Table 2 provides a summary of the biomarker tests currently included in this policy that have FDA clearance.

Table 2. Select Biomarker Tests for Detection of Heart or Renal Allograft Rejection Cleared by the U.S. FDA

Test	Manufacturer	FDA Clearance Type, Product Number	FDA Clearance Date	Indicated Use
Heartsbreath™‡	Menssana Research	Humanitarian device exemption, H030004	2004	To 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.
AlloMap®‡ Molecular Expression Testing	CareDx, formerly XDx	510(k), k073482	2008	The test is to be used 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.

FDA: Food and Drug Administration.

Laboratory Developed Tests
There are also commercially available laboratory-developed biomarker tests for the detection of heart and renal allograft rejection. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. To-date, AlloSure (CareDx) renal and lung and Prospera (Natera) renal dd-cfDNA tests are regulated under the Clinical Laboratory Improvement Amendments standards.

These LDTs have not been cleared or approved by the FDA.

Other Tests
Other commercially available LDTs without FDA clearance or approval for use have been excluded from this evidence review when studies reporting on the clinical validity of the marketed version of the test could not be identified and/or where the test is marketed for research use only. Excluded tests and their descriptions are summarized for reference purposes in Table 3.

Table 3. Biomarker Tests Excluded from Review

Test	Manufacturer	Technology	Indications for Use
KidneyCare®‡	CareDx	dd-cfDNA and GEP	Available as a research tool through the OKRA Registry.
AlloSeq®‡ HCT	CareDx	NGS	To aid in the assessment of engraftment following HCT via NGS analysis of 202 biallelic SNPs. The fraction of recipient and donor genomic DNA is reported. The test is marketed for research use only.
AlloSeq®‡ Tx17	CareDx	NGS	An NGS test utilizing Hybrid Capture Technology conducted pre-transplant to identify optimal transplant matches. The test sequences full HLA genes and other transplant-associated genes (KIR, MICA/B, C4, HPA, ABO). This test is marketed for research use only.

Viracor TRAC®‡	Eurofins	dd-cfDNA	To aid in the diagnosis of solid organ transplant rejection via NGS analysis. The fraction of dd-cfDNA is reported.[1]
MMDx®‡ Heart	Kashi Clinical Laboratories	Tissue-based microarray	Tissue-based microarray mRNA gene expression test of 1283 genes post-transplant to provide a probability score of rejection as a complement to conventional biopsy processing. The test is not marketed to provide information for the diagnosis, prevention, or treatment of disease or to aid in the clinical decision-making process.

dd-cfDNA: donor-derived cell-free DNA; GEP: gene expression profiling; HCT: hematopoietic cell transplantation; HLA: human leukocyte antigen; MMDx: molecular microscope diagnostic system; NGS: next-generation sequencing; OKRA: Outcomes in KidneyCare in Renal Allografts; SNP: single-nucleotide polymorphism; TRAC: transplant rejection allograft check. Published studies reporting on the clinical validity of the marketed version of the test were not identified.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Clinical assessment and noninvasive imaging of chronic heart failure can be limited in accurately diagnosing patients with heart failure because symptoms and signs can poorly correlate with objective methods of assessing cardiac dysfunction. For management of heart failure, clinical signs and symptoms (eg, shortness of breath) are relatively crude markers of decompensation and occur late in the course of an exacerbation. Thus, circulating biomarkers have potential benefit in heart failure diagnosis and management.

In transplant recipients, despite the progress in immunosuppressant therapy, the risk of rejection remains. Diagnosis of allograft rejection continues to rely on clinical monitoring and histologic confirmation by tissue biopsy. However, due to limitations of tissue biopsy, including a high degree of interobserver variability in the grading of results and its potential complications, less invasive alternatives have been investigated. Several laboratory-tested biomarkers of transplant rejection have been evaluated and are commercially available for use. The laboratory tests for heart transplant rejection currently evaluated in this policy include the Heartsbreath test, which measures breath markers of oxidative stress; the AlloMap test, which uses gene expression profiling (GEP); and the HeartCare test, which combines AlloMap GEP testing with the AlloSure Heart test for donor-derived cell-free DNA (dd-cfDNA). Also included in this policy are the AlloSure dd-cfDNA tests for assessment of renal and lung transplant rejection.

Summary of Evidence
For individuals who have a heart transplant who receive a measurement of volatile organic compounds to assess cardiac allograft rejection, the evidence includes a diagnostic accuracy study. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. The published study found that, for identifying grade 3 (now grade 2R) rejection, the 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 that the technology results in an improvement in the net health outcome.

For individuals who have a heart transplant who receive dd-cfDNA testing to determine acute rejection, the evidence includes diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. Evidence from 3 studies suggests that the dd-cfDNA fraction is elevated in acute rejection, but optimal fraction cut-offs for detection of acute rejection have not been established. Using dd-cfDNA thresholds ranging from 0.12% to 0.32% resulted in NPVs ranging from 82% to 98% and AUCs ranging from 0.61 to 0.86 in 3 studies. At present, no studies evaluating the clinical utility for the measurement of dd-cfDNA for heart transplant rejection have been identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a heart transplant who receive GEP to assess cardiac allograft rejection, the evidence includes 2 diagnostic accuracy studies and several RCTs evaluating clinical utility. Relevant outcomes are OS, 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 NPVs were relatively high (ie, at least 88%), the performance characteristics were only calculated based on few 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 post transplant and 4.3% for patients more than 6 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 (eg, lack of blinding); further, the IMAGE study failed to provide evidence that GEP offers an 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 that the technology results in an improvement in the net health outcome.

For individuals who have a heart transplant who receive GEP with testing of dd-cfDNA to assess cardiac allograft rejection, the evidence includes 1 retrospective analysis of the HeartCare test and 1 diagnostic accuracy study of the AlloSure dd-cfDNA component of the HeartCare test. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. The HeartCare analysis reported a 12.7% reduction in endomyocardial biopsy volume among patients undergoing routine surveillance. However, this observation is limited by lack of reporting on long-term health outcomes and incomplete assessment of diagnostic performance for combined testing, as patients with negative dd-cfDNA scores did not undergo biopsy regardless of GEP score per study protocol. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a renal transplant who are undergoing surveillance or have clinical suspicion of allograft rejection who receive testing of dd-cfDNA to assess renal allograft rejection, the evidence includes diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. Two studies examined the diagnostic performance of dd-cfDNA for detecting

moderate-to-severe rejection; the NPV was moderately high (75% to 84%), and performance characteristics were calculated on cases of active transplant rejection. In one study, the threshold indicating a positive test was not prespecified. A subsequent smaller single-center study that explored variation in clinical validity based on different rejection mechanisms found the strongest performance characteristics for AlloSure with antibody-mediated rejection. Using dd-cfDNA threshold values from ≥0.5% to ≥1%, the Allosure test established a range of sensitivities from 59% to 86% and specifities of 72% to 100% for the detection of graft rejection. This corresponded to PPVs ranging from 61% to 77% and NPVs from 75% to 84%. A retrospective single-center study of the Prospera dd-cfDNA test reported a PPV and NPV of 52% and 95%, respectively, for detection of active rejection among a combined cohort of patients undergoing surveillance or for-cause biopsies, using the 1% dd-cfDNA threshold previously proposed for the AlloSure test. A second, prospective Prospera study reported PPVs of 68% and 71% and NPVs 91% and 83% using combined dd-cfDNA fraction and absolute quantity compared with two different reference standards. Larger prospective studies validating the dd-cfDNA thresholds for active rejection are needed to develop conclusions for each test. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a lung transplant who receive testing of dd-cfDNA to assess lung allograft rejection, the evidence includes 4 small diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. One study examined the diagnostic performance of dd-cfDNA testing at a threshold of 0.87% for detecting acute cellular rejection, yielding a PPV of 34.1% and a NPV of 85.5%. A second study reported a PPV of 43.3% and NPV of 83.6% for an aggregate rejection cohort composed of patients with acute cellular rejection, antibody-mediated rejection, and CLAD. In the third study, using a dd-cfDNA cut-off of 1.0%, PPV was 51.9% and NPV was 97.3% for acute rejection, and 43.6%, and 91.0% for acute rejection, CLAD/NRAD or infection. One study that used dd-cfDNA testing as part of a home surveillance program found a PPV 43.4% and NPV 96.5% for detection of ACR, AMR or infection, but when limited to patients with a contemporaneous reference standard surveillance bronchoscopy independent of dd-cfDNA level, PPV 66.7% and NPV was 79.2%. All 4 studies were limited by small sample sizes, and no clinical utility studies were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input
In response to requests, input was received from 7 academic medical centers and 1 specialty society while this policy was under review in 2012. Input was mixed on whether AlloMap should be investigational. Four reviewers agreed with the investigational status, 1 disagreed, and 3 indicated it was a split decision/other. Reviewers generally agreed that the sensitivity and specificity have not yet been adequately defined for AlloMap and that the negative predictive value was not sufficiently high to preclude the need for biopsy. There was mixed input about the need for surveillance cardiac biopsies to be performed in the absence of clinical signs and/or symptoms of rejection.

2008 Input
In response to requests, input was received from 2 academic medical centers and 2 physician specialty societies while this policy was under review in 2008. Three reviewers agreed that these approaches for monitoring heart transplant rejection are considered investigational. The American College of Cardiology disagreed with the policy, stating that the College considers the available laboratory tests to have good potential to diagnose heart transplant rejection and reduce the frequency of invasive biopsies performed on heart transplant patients, although questions remained as to their role in clinical practice.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology et al

In 2022, the American College of Cardiology, American Heart Association, and Heart Failure Society issued updated a guideline for the management of heart failure. The 2022 guideline replaced a 2013 guideline and a 2017 focused guideline update. The guideline states measurement of natriuretic peptide levels may be useful for diagnosis, risk stratification, and prognosis of heart failure. The use of soluble suppression of tumorigenicity-2 is not discussed specifically, though the guideline notes that "a widening array of biomarkers including markers of myocardial injury, inflammation, oxidative stress, vascular dysfunction, and matrix remodeling have been shown to provide incremental prognostic information over natriuretic peptides but remain without evidence of an incremental management benefit."

American Society of Transplant Surgeons

In 2023, the American Society of Transplant Surgeons (ASTS) issued a position statement on the role of dd-cfDNA in kidney transplant surveillance.The following recommendations regarding the clinical utility and decision analysis were issued:

- "The most data have been accumulated in adult transplant recipients, and these recommendations are therefore most applicable to adult patient populations.
- We suggest that clinicians consider measuring serial dd-cfDNA levels in kidney transplant recipients with stable renal allograft function to exclude the presence of subclinical antibody-mediated rejection.
- We recommend that clinicians measure dd-cfDNA levels in kidney transplant recipients with acute allograft dysfunction to exclude the presence of rejection, particularly antibody-mediated rejection (ABMR).
- We do not recommend the use of blood gene expression profiling (GEP) in kidney transplant recipients for the purpose of diagnosing or excluding sub-clinical rejection, as adequate evidence supporting such use is still lacking.
- We do not recommend the use of blood GEP to diagnose or exclude the presence of acute graft rejection in kidney transplant recipients with acute allograft dysfunction given the paucity of data to support this practice.
- We recommend that dd-cfDNA may be utilized to rule out subclinical rejection in heart transplant recipients.

- We recommend that clinicians utilize peripheral blood GEP as a non-invasive diagnostic tool to rule out acute cellular rejection in stable, low-risk, adult heart transplant recipients who are over 55 days status post heart transplantation."

"Caveats and recommendations for future studies:

- None of these recommendations should be construed as recommending one biomarker over another in the same diagnostic niche.
- We strongly recommend ongoing clinical studies to clarify the scenarios in which molecular diagnostic studies should be utilized.
- We specifically recommend that studies be carried out to evaluate the potential role of dd-cfDNA surveillance in kidney transplant recipients to improve long-term allograft survival."

International Society of Heart and Lung Transplantation

In 2022, the International Society of Heart and Lung Transplantation issued updated guidelines for the care of heart transplant recipients. The guidelines included the following recommendations (see Table 4).

Table 4. Guidelines for Postoperative Care of Heart Transplant Recipients

Recommendation	**COR**	**LOE**
"It is reasonable to perform periodic EMB during the first 3 to 12 postoperative months for surveillance of HT rejection	IIa	C
“After the first post-operative year, it is reasonable to continue EMB surveillance in patients who are at higher risk for late acute rejection	IIa	C
"Gene Expression Profiling (GEP) (i.e., AlloMap) of peripheral blood can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR to reduce the frequency of EMB. Data in children does not allow a general recommendation of GEP as a routine tool at present."	IIa	B

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 5).

Table 5. Guidelines for Biopsy in Renal Transplant Recipients

Recommendation	SOR	LOE
"We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine."	Level 1	C
"We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection."	Level 2	D
"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, HeartCare, AlloSure, Prospera Assay there are no national coverage determinations. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Active Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
AlloMap			
NCT01833195[a]	Outcomes AlloMap Registry: the Long-term Management and Outcomes of Heart Transplant Recipients With AlloMap Testing (OAR)	2444	Feb 2020 (unknown)
NCT02178943[a]	Utility of Donor-Derived Cell-free DNA in Association With Gene-Expression Profiling (AlloMap®) in Heart Transplant Recipients (D-OAR)	100	Feb 2020 (unknown)
HeartCare			
NCT05459181[a]	Molecular Outcome Surveillance Using AlloSure and AlloMap Guided Immunomodulation in Cardiac Transplant (MOSAIC)	930	Sep 2025
NCT03695601[a]	Surveillance HeartCare Outcomes Registry (SHORE)	3450	Jun 2027 (active, not recruiting)
AlloSure (Kidney)			

NCT04566055[a]	Assessing AlloSure dd-cfDNA Monitoring Insights of Renal Allografts With Longitudinal Surveillance (ADMIRAL)	1000	Oct 2020 (active, not recruiting)
NCT04057742a	AlloSure for the Monitoring of Antibody Mediated Processes After Kidney Transplantation (All-MAP)	69	Dec 2024 (recruiting)
NCT03326076[a]	Evaluation of Patient Outcomes From the Kidney Allograft Outcomes AlloSure Registry (KOAR)	4000	Dec 2025 (recruiting)
NCT04601155[a]	Transition of Renal Patients Using AlloSure Into Community Kidney Care (TRACK)	3500	Sep 2026 (recruiting)
AlloSure (Lung)			
NCT04318587[a]	Assessment of Donor Derived Cell Free DNA and Utility in Lung Transplantation	50	Sep 2023 (active, not recruiting)
NCT05050955[a]	Allosure Lung Assessment and Metagenomics Outcomes Study (ALAMO)	1500	Dec 2026 (recruiting)
Prospera (Kidney)			
NCT04239703[a]	Trifecta-Kidney cfDNA-MMDx Study: Comparing the DD-cfDNA Test to MMDx Microarray Test, Central HLA Antibody Test, and Histology	300	Dec 2024 (recruiting)
NCT04091984[a]	The PROspera Kidney Transplant ACTIVE Rejection Assessment Registry (ProActive)	5000	Oct 2027 (recruiting)
NCT03984747[a]	Study for the Prediction of Active Rejection in Organs Using Donor-derived Cell-free DNA Detection (SPARO)	500	Oct 2028 (recruiting)
Prospera (Heart)			

NCT04707872[a]	Trifecta-Heart cfDNA-MMDx Study: Comparing the DD-cfDNA test to MMDx Microarray Test and Central HLA Antibody Test	300	Jul 2024 (recruiting)
NCT05081739[a]	Donor-Derived Cell-free DNA to Detect Rejection in Cardiac Transplantation (DETECT)	600	Jan 2025 (not yet recruiting)
NCT05205551	Prospera Test Evaluation in Cardiac Transplant (ProTECT)	1000	Dec 2027 (recruiting)
Prospera (Lung)			
NCT05837663a	Trifecta-Lung cfDNA-MMDx Study: Comparing the Dd-cfDNA Test to MMDx Microarray Test and Central HLA Antibody Test	600	Dec 2025 (recruiting)
NCT05170425[a]	Observational Registry Study With Sub-analysis (Patients Previously Randomized to LAMBDA 001) to Assess Prospera™ Performance for Detection of CLAD After Lung Transplant (LAMBDA 002)	1000	Dec 2029 (not yet recruiting)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 01/31/2005
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12/07/2004	Medical Director review
12/14/2004	Medical Policy Committee review
01/31/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
01/10/2007	Medical Director review
01/17/2007	Medical Policy Committee approval. New policy statement added regarding evaluation of genetic expression in the peripheral blood.
01/07/2009	Medical Director review
01/14/2009	Medical Policy Committee approval. No change to coverage.
01/07/2010	Medical Policy Committee approval
01/20/2010	Medical Policy Committee Implementation approval. No change to coverage.
01/06/2011	Medical Policy Committee approval
01/19/2011	Medical Policy Committee Implementation approval. No change to coverage.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Added " Based on review of available data, the Company considers AlloMap molecular expression testing as a non-invasive method of determining the risk of rejection in heart transplant recipients to be eligible for coverage." Used to be considered investigational.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Added grade 2R category to policy statement.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017 Medical Policy Committee review
12/20/2017 Medical Policy Implementation Committee approval. No change to coverage.
12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. 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.
12/05/2019 Medical Policy Committee review
12/11/2019 Medical Policy Implementation Committee approval. No change to coverage.
09/03/2020 Medical Policy Committee review
09/09/2020 Medical Policy Implementation Committee approval. Added criteria for AlloMap. Added the myTAIHEART assay as investigational.
12/11/2020 Coding update
09/02/2021 Medical Policy Committee review
09/08/2021 Medical Policy Implementation Committee approval. Investigational criteria clarified.
09/30/2021 Coding update
01/06/2022 Medical Policy Committee review
01/12/2022 Medical Policy Implementation Committee approval. Use of peripheral blood measurement of dd-cf DNA testing for transplant rejection status is considered investigational for the following including but not limited to:

- The use of peripheral blood measurement of dd-cf DNA (e.g., AlloSure, Prospera) 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;
- The use of peripheral blood gene expression profile tests in combination with peripheral blood measurement of dd-cf DNA (e.g., HeartCare) 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;
- The use of peripheral blood measurement of dd-cf DNA (e.g., AlloSure, Viracor) in the management of patients after lung transplantation, including but not limited to the detection of acute lung transplant rejection or lung transplant graft dysfunction;
- The use of the myTAIHEART assay in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection.

Title changed to Laboratory Tests Post Transplant.

03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Removed Pleximark, myTAIHEART, and MMDx—Kidney based on Avalon partnership policy M2091.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Added the use of peripheral blood measurement of dd-cfDNA in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection as investigational.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Removed ST2 assay from policy. References and body of policy updated to reflect this change. Supplemental information updated.

Next Scheduled Review Date: 11/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

Laboratory Tests Post Transplant

Policy # 00148
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0087U, 0118U, 81479, 81595 Delete code effective 12/01/2023: 86849
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety,

effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.