Medical Coverage Policy | Laboratory Tests Post Transplant and for Heart Failure

EFFECTIVE DATE: 07|01|2022
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OVERVIEW

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, 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 following test are addressed in this policy:

- AlloMap (CareDx)
- AlloSure Heart (CareDx)
- AlloSure Kidney (CareDx)
- AlloSure Lung (CareDx)
- HeartCare (CareDx)
- Heartsbreath (Menssana Research)
- myTAIHEART (TAI Diagnostics)
- Presage ST2 Assay (Critical Diagnostics)
- Prospera (Natera)
- Viracor TRAC dd-cfDNA (Viracor Eurofins)

MEDICAL CRITERIA

Medicare Advantage Plans

AlloSure Heart

AlloSure Heart may be considered medically necessary when all of the following criteria are met:

- It is used in conjunction with AlloMap,
- To assess the probability of allograft rejection in heart transplant recipients with clinical suspicion of rejection,
- To inform clinical decision-making about the necessity of a heart biopsy in such patients at least 55 days post-transplant in conjunction with standard clinical assessment.

AlloSure Kidney

AlloSure Kidney may be considered medically necessary when all of the following criteria are met:

- It is used to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection,

- 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.

Prospera and Viracor TRAC dd-cfDNA
Prospera and Viracor TRAC dd-cfDNA may be considered medically necessary when all of the following criteria are met:

- The test must provide information about at least one of the two following clinical status determinations:
  - Active Rejection (AR) status, OR
  - Cellular or Antibody-mediated rejection (ACR or AMR) status
- The intended use of the test must be:
  - To assist in the evaluation of adequacy of immunosuppression, wherein a non-invasive or minimally invasive test can be used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision regarding immunosuppression, OR
  - As a rule-out test for AR in validated populations of patients with clinical suspicion of rejection with a non-invasive or minimally invasive test to make a clinical decision regarding obtaining a biopsy, OR
  - For further evaluation of allograft status for the probability of allograft rejection after a physician assessed pretest, OR
  - To assess rejection status in patients that have received a biopsy, but the biopsy results are inconclusive or limited by insufficient material.
- The test is being used in a patient who is part of the population in which the test was analytically validated and has demonstrated clinical validity (CV).
- For a given patient encounter, only one molecular test for assessing allograft status may be performed UNLESS a second test, meeting all the criteria established herein, is reasonable and necessary as an adjunct to the first test.
- The test successfully completes a Technical Assessment that will ensure that analytical validity (AV), CV, and clinical utility criteria set in this policy are met to establish the test as reasonable and necessary.

Commercial Products
Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans
Prior authorization is required for the following tests:

- AlloSure Heart
- AlloSure Kidney
- Prospera
- Viracor TRAC dd-cfDNA

Commercial Products
Not applicable

Medicare Advantage Plans and Commercial Products
There is no specific CPT coding for some of the services referenced in this policy. Therefore, 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.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans

The following test is covered:

- AlloMap

The following tests may be considered medically necessary when the medical criteria above are met:

- AlloSure Heart
- AlloSure Kidney
- HeartCare*
- Prospera
- Viracor TRAC dd-cfDNA

***Note:** HeartCare provides a comprehensive assessment of graft rejection by combining AlloMap Heart gene expression profiling with AlloSure® Heart dd-cfDNA. Therefore, as AlloMap is a covered service for Medicare Advantage Plans, HeartCare may be medically necessary dependent on the medical necessity determination of AlloSure Heart, in accordance with the medical criteria found above.

The following tests are not covered as the evidence is insufficient to determine the effects of the technology on health outcomes:

- AlloSure Lung
- Heartsbreath
- myTAIHEART
- Presage ST2 Assay

Commercial Products

The following tests are not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- AlloMap
- AlloSure Heart
- AlloSure Kidney
- AlloSure Lung
- HeartCare
- Heartsbreath
- myTAIHEART
- Presage ST2 Assay
- Prospera

- Viracor TRAC dd-cfDNA

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 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 from 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 also are 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.7, 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 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 prognosis of heart failure patients, with elevated blood levels portending poorer prognosis.

In addition to diagnosing and assessing 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.

Suppression of Tumorigenicity-2 Protein Biomarker
A protein biomarker, ST2, has elicited interest as a potential aid to predict prognosis and manage therapy of heart failure. This protein is a member of the interleukin-1 (IL-1) receptor family. It is found as a transmembrane isoform (ST2L) and a soluble isoform (sST2), both of which have circulating IL-33 as their primary ligand. ST2 is a unique biomarker that has pluripotent effects in vivo. Thus, binding between IL-33 and ST2L is believed to have an immunomodulatory function via T-helper type 2 lymphocytes and was initially described in the context of cell proliferation, inflammatory states, and autoimmune diseases. However, the IL-33/ST2L signaling cascade is also strongly induced through mechanical strain of cardiac fibroblasts or cardiomyocytes. The net result is mitigation of adverse cardiac remodeling and myocardial fibrosis, which are key processes in the development of heart failure. The soluble isoform of ST2 is produced by lung epithelial cells and cardiomyocytes and is secreted into circulation in response to exogenous stimuli, mechanical stress, and cellular stretch. This form of ST2 binds to circulating IL-33, acting as a "decoy," thus inhibiting the IL-33-associated antiremodeling effects of the IL-33/ST2L signaling pathway. Thus, on a

biologic level, IL-33/ST2L signaling plays a role in modulating the balance of inflammation and neurohormonal activation and is viewed as pivotal for protection from myocardial remodeling, whereas sST2 is viewed as attenuating this protection. In the clinic, blood concentrations of sST2 appear to correlate closely with adverse cardiac structure and functional changes consistent with remodeling in patients with heart failure, including abnormalities in filling pressures, chamber size, and systolic and diastolic function.

An enzyme-linked immunosorbent-based assay is commercially available for determining sST2 blood levels (Presage ST2 Assay). The manufacturer claims a limit of detection of 1.8 ng/mL for sST2, and a limit of quantification of 2.4 ng/mL, as determined according to Clinical and Laboratory Standards Institute guideline EP-17-A. Mueller and Dieplinger (2013) reported a limit of detection of 2.0 ng/mL for sST2 in their study. In the same study, the assay had a within-run coefficient of variation of 2.5% and a total coefficient of variation less than 4.0%, demonstrated linearity within the dynamic range of the assay calibration curve, and exhibited no relevant interference or cross-reactivity.

The ST2 biomarker is not intended to diagnosis heart failure because it is a relatively nonspecific marker that is increased in many other disparate conditions that may be associated with acute or chronic manifestations of heart failure. Although the natriuretic peptides (BNP, NT-proBNP) reflect different physiologic aspects of heart failure compared with sST2, they are considered the reference standard biomarkers when used with clinical findings to diagnose, prognosticate, and manage heart failure and as such are the comparator to sST2.

HEART TRANSPLANT REJECTION

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

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

In addition to those below, 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.

Heartsbreath Test
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.

Medicare Advantage Plans and Commercial Products
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 that the technology results in an improvement in the net health outcome.

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 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.

Medicare Advantage Plans
AlloMap®, an In Vitro Diagnostic Multivariate Index assay (IVDMIA) test service performed in a single laboratory, is FDA approved to aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment.

AlloMap® is marketed by CareDx® for cardiac transplantation as a noninvasive means to assess allograft rejection status. AlloMap® has been characterized as a "rule-out" test for rejection that can be complemented by a cell-free DNA "rule-in" test. The utility of the combination of these 2 tests when used together was assessed and found that together these tests enhance the accuracy of assessing rejection status than either test alone.

A test using Gene-Expression Profiling, AlloMap® is marketed by CareDx® for cardiac transplantation and has been covered under the Centers for Medicare and Medicaid Services (CMS) MolDX program as a non-invasive means to assess allograft rejection status.

Commercial Products

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 that the technology results in an improvement in the net health outcome.

AlloSure Heart

The premise for AlloSure is that rejection entails injury, including increased cell death in the allograft, leading to increased donor-derived cell-free DNA (dd-cfDNA) released into the bloodstream. The AlloSure test for dd-cfDNA detected in the blood of transplant recipients has been developed as a noninvasive marker for diagnosis of graft rejection. The AlloSure assay is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to accurately quantify dd-cfDNA in transplant recipients without separate genotyping of donor or recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs and can be completed within 3 days of peripheral blood collection, a practical turnaround time for management of transplant recipients. AlloSure assay results are reported as the percentage of dd-cfDNA in total cfDNA.

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.

Medicare Advantage Plans

It is well accepted within the renal and cardiac transplant communities that immunosuppression management is an important component of post-transplant care to both optimize graft longevity while avoiding side effects and toxicity of immunosuppressive therapies. Graft assessment is an important decision tool used to help clinicians optimize immunosuppressive treatment. The gold standard for assessing rejection or a solid organ allograft rejection or injury has historically and remains a biopsy in conjunction with serologic criteria. However, given the invasive nature and risks associated with a biopsy, tests that can potentially mitigate the need for a biopsy while still providing clinicians with actionable information that can be used to help optimize immunosuppressive therapy are reasonable and necessary. Thus there is adequate evidence to support that the AlloSure assay when used in combination provides incremental information to change clinician management in a way that will be expected to improve outcomes.

Commercial Products
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 diagnostic accuracy of the AlloSure dd-cfDNA test was assessed separately in the Utility of Donor-Derived Cell Free DNA in Association With Gene Expression Profiling (D-OAR) study, revealing high NPVs (>96.6%). However, at a dd-cfDNA cutoff of 0.2%, PPVs were low overall (8.9%), in surveillance patients (8.1%), and in patients with clinical suspicion of rejection (11.6%). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Presage ST2 Assay
In addition to its use as a potential aid to predict prognosis and manage therapy of heart failure, elevated serum ST2 levels have also been associated with increased risk of antibody-mediated rejection following heart transplant. For this reason, ST2 has also been proposed as a prognostic marker post heart transplantation and as a test to predict acute cellular rejection (graft-versus-host disease). The Presage ST2 Assay, described above, is a commercially available sST2 test that has been investigated as a biomarker of heart transplant rejection.

Medicare Advantage Plans and Commercial Products
For individuals who have chronic heart failure who receive the sST2 assay to determine prognosis and/or to guide management, the evidence includes correlational studies and 2 meta-analyses. Relevant outcomes are overall survival, quality of life, and hospitalization. Most of the evidence is from reanalysis of existing randomized controlled trials and not from studies specifically designed to evaluate the predictive accuracy of sST2, and prospective and retrospective cross-sectional studies made up a large part of 1 meta-analysis. Studies have mainly found that elevated sST2 levels are statistically associated with elevated risk of mortality. A pooled analysis of study results found that sST2 significantly predicted overall mortality and cardiovascular mortality. Several studies, however, found that sST2 test results did not provide additional prognostic information compared with N-terminal pro B-type natriuretic peptide levels. Moreover, no comparative studies were identified on the use of the sST2 assay to guide management of patients diagnosed with chronic heart failure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart transplantation who receive sST2 assay to determine prognosis and/or to predict acute cellular rejection, the evidence includes a small number of retrospective ~~observational~~ studies on the Presage ST2 Assay. Relevant outcomes are overall survival, morbid events, and hospitalization. No prospective studies were identified that provide high-quality evidence on the ability of sST2 to predict transplant outcomes. One retrospective study (n = 241) found that sST2 levels were associated with acute cellular rejection and mortality; another study (n = 26) found that sST2 levels were higher during an acute rejection episode than before rejection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

myTAIHEART Biomarker
Using proprietary myTAIHEART software, the myTAIHEART test uses multiplexed, high-fidelity amplification followed by allele-specific qPCR of a panel of 94 highly informative bi-allelic single nucleotide polymorphisms (SNPs) and two controls to quantitatively genotype cell free DNA in the patient's plasma after cardiac transplant, and accurately distinguish "donor specific" cell free DNA originating from the engrafted heart from "self-specific" cell free DNA originating from the recipient's native cells. The ratio of donor specific cell free DNA to total cell free DNA is reported as the donor fraction (%) and categorizes the patient as at low or increased risk of moderate (grade 2R) to severe (grade 3R) acute cellular rejection: low

donor fractions indicate less damage to the transplanted heart and a lower risk for rejection, while increased donor fractions indicate more damage to the transplanted heart and an increased risk for rejection. Testing with myTAIHEART does not require a donor specimen. The test is indicated for use in heart transplant recipients who are 2 months of age or older and ≥ 8 days post-transplant, restricted to use in single organ post-heart transplant patients, and is contraindicated in patients who:

- are pregnant
- currently have or in the past have had another transplanted organ (solid organ or allogeneic bone marrow)
- have post-transplant lymphoproliferative disease
- have cancer or have had cancer within the previous 2 years
- are on mechanical circulatory support
- are closely related to the transplant donor

Medicare Advantage Plans and Commercial Products
For individuals who have heart transplantation who receive myTAIHEART assay to determine acute cellular rejection, the evidence includes observational studies. A validation study using 158 matched endomyocardial biopsy-plasma pairs from 76 pediatric and adult heart transplant recipients (ages 2 months or older, and 8 days more post-transplant) found a donor-specific fraction cutoff (0.32%) that produced a 100% negative predictive value for Grade 2 or higher acute cellular rejection. A prospective observational blinded study (n=174; pediatric=101, adult=73) using biopsy-paired samples found that myTAIHEART level was associated with acute cellular and antibody-mediated rejection in both adult and pediatric heart transplant populations, and that an optimal donor fraction threshold (0.3%) ruled out the presence of either acute cellular rejection or antibody-mediated rejection. Both studies received industry funding. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 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 Kidney

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.

Medicare Advantage Plans
The premise for AlloSure is that rejection entails injury, including increased cell death in the allograft, leading to increased donor-derived cell-free DNA (dd-cfDNA) released into the bloodstream. The A AlloSure® test for dd-cfDNA detected in the blood of transplant recipients has been developed as a noninvasive marker for diagnosis of graft rejection. The AlloSure® assay is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to accurately quantify dd-cfDNA in transplant recipients without separate genotyping of donor or recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs and can be completed within 3 days of peripheral blood collection, a practical turnaround time for management of transplant recipients. AlloSure assay results are reported as the percentage of dd-cfDNA in total cfDNA.

It is well accepted within the renal and cardiac transplant communities that immunosuppression management is an important component of post-transplant care to both optimize graft longevity while avoiding side effects and toxicity of immunosuppressive therapies. Graft assessment is an important decision tool used to help clinicians optimize immunosuppressive treatment. The gold standard for assessing rejection or a solid organ allograft rejection or injury has historically and remains a biopsy in conjunction with serologic criteria. However, given the invasive nature and risks associated with a biopsy, tests that can potentially mitigate the need for a biopsy while still providing clinicians with actionable information that can be used to help optimize immunosuppressive therapy are reasonable and necessary. Thus there is adequate evidence to support that the AlloSure assay when used in combination provides incremental information to change clinician management in a way that will be expected to improve outcomes.

Commercial Products
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 small diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. One study examined the diagnostic performance of dd-cfDNA for detecting moderate-to-severe rejection; the NPV 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. 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. 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. 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.

Prospera
Prospera Kidney (Natera) is a commercially available assay that uses massively multiplexed PCR (mmPCR) followed by next-generation sequencing (NGS) to quantify the fraction of dd-cfDNA in renal transplant recipients. Donor versus recipient cfDNA is differentiated via an advanced bioinformatics analysis of >13,000 single-nucleotide polymorphisms (SNPs) without the need for prior recipient or donor genotyping or computational adjustments for related donors. The manufacturer recommends use of the test when there is clinical suspicion of active rejection and for regular surveillance of subclinical rejection., 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 ddcfDNA relative to total cfDNA is reported, with detection of greater than or equal to 1% dd-cfDNA indicating increased risk for active rejection. The percent dd-cfDNA change between tests is also reported.

Viracor TRAC dd-cfDNA
The Viracor TRAC test is intended to assess the probability of allograft rejection in transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of biopsy in such patients at least 2 weeks posttransplant in conjunction with standard clinical assessment.

Medicare Advantage Plans
It is also well accepted within the transplant community that immunosuppression management is an important component of post-transplant care to both optimize graft longevity while avoiding side effects and toxicity of immunosuppressive therapies. Graft assessment is an important decision tool used to help clinicians optimize immunosuppressive treatment. The gold standard for assessing rejection or injury has historically been and remains a biopsy in conjunction with serologic criteria. However, given the invasive nature and risks associated with a biopsy, tests that can potentially mitigate the need for a biopsy while still providing clinicians with actionable information that can be used to help optimize immunosuppressive therapy are reasonable and necessary. Additionally, ongoing studies have supported that cfDNA and GEP can accurately determine allograft status in several organ types, and that molecular characterization can both precede and enhance histologic findings. As such, these approaches, as a service type, are reasonable and necessary for graft assessment.

Commercial Products
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 small diagnostic accuracy studies. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. One study examined the diagnostic performance of dd-cfDNA for detecting moderate-to-severe rejection; the NPV 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. 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. 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. 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.

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 FEV1. 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 Lung

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.

Medicare Advantage Plans and Commercial Products

For individuals with a lung transplant who receive testing of dd-cfDNA to assess lung allograft rejection, the evidence includes 2 small diagnostic accuracy studies utilizing biorepository samples. Relevant outcomes are OS, test validity, morbid events, and hospitalizations. One study examined the diagnostic performance of AlloSure 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 chronic lung allograft dysfunction. These studies have raised concerns regarding the ability of dd-cfDNA testing to discriminate between rejection and infection or injury, and larger prospective clinical validation studies are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

The following CPT code is covered for Medicare Advantage Plans 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

The following CPT codes are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products.

This code can be used for Presage® ST2 Assay:

83006 Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)

This code can be used for myTAIHEART:

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 medically necessary for Medicare Advantage Plans when medical criteria above are met and is not medically necessary for Commercial Products.

This code can be used for Viracor TRAC™ dd-cfDNA:

0118U Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA

The following Unlisted CPT code requires prior authorization for Medicare Advantage Plans and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.

81479 Unlisted molecular pathology procedure

RELATED POLICIES

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, May 2022
Provider Update, April 2021
Provider Update, June 2020
Provider Update, April 2019

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