BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.01.68 Laboratory Tests Post Transplant and for Heart Failure

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Related Policies:

7.03.08 - Heart/Lung Transplant
7.03.09 - Heart Transplant

Laboratory Tests Post Transplant and for Heart Failure

Description

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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.

Noninvasive Heart Transplant Rejection Tests

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.

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.[22,] All AlloMap testing is performed at the CareDx reference laboratory in California.

HeartCare

Cell-free DNA (cfDNA), released by damaged cells, is normally present in healthy individuals.[23,] 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.

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 an increased risk of antibody-mediated rejection following a 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.

myTAI$_{HEART}$ Biomarker

Using proprietary myTAI$_{HEART}$ software, the myTAI$_{HEART}$ 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.[24,] 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 myTAI$_{HEART}$ 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

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.[25,26,]

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%.[27,]

Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis.[28,] 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.[29,]

Kidney biopsies allow for diagnosis of acute and chronic graft rejection, which may be graded using the Banff Classification.[30,31,] 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 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.[32,] 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.[33,] 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.

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.[34,35,] 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.[36,] 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.[37,

OBJECTIVE

The objective of this evidence review is to determine whether the measurement of various selected biomarkers improves the detection of allograft rejection in transplant patients or in the diagnosis and management of heart failure, thus improving net health outcomes.

POLICY STATEMENT

The use of the Presage ST2 Assay to evaluate the prognosis of patients diagnosed with chronic heart failure is considered **investigational**.

The use of the Presage ST2 Assay to guide management (eg, pharmacologic, device-based, exercise) of patients diagnosed with chronic heart failure is considered **investigational**.

The use of the Presage ST2 Assay in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection, is considered **investigational.**

The use of the myTAI$_{HEART}$ assay in the post cardiac transplantation period, including but not limited to predicting prognosis and predicting acute cellular rejection, is considered **investigational.**

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

The use of peripheral blood gene expression profile tests alone or in combination with peripheral blood measurement of donor-derived cell-free DNA (dd-cfDNA) in the management of patients after heart transplantation, including but not limited to the detection of acute heart transplant rejection or heart transplant graft dysfunction, is considered **investigational**.

The use of peripheral blood measurement of dd-cfDNA 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**.

The use of peripheral blood measurement of dd-cfDNA 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, is considered **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.

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.[21, 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

The U.S. Food and Drug Administration (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. Food and Drug Administration

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.
Presage ST2 Assay kit	Critical Diagnostics	510(k), k093758	2011	For use with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure

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.

myTAI$_{HEART}$ is also a laboratory developed test (LDT) developed for clinical diagnostic performance exclusively in the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) accredited TAI Diagnostics Clinical Reference Laboratory.[24,] This test was developed and its performance characteristics were determined by TAI Diagnostics.

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.
MMDx Kidney	Kashi Clinical Laboratories	Tissue-based microarray	Tissue-based microarray mRNA gene expression test of 1494 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.

[1] Published studies reporting on the clinical validity of the marketed version of the test were not identified.

RATIONALE

Summary of Evidence

For individuals who have chronic heart failure who receive the soluble suppression of tumorigenicity-2 (sST2) assay to determine prognosis and/or to guide management, the evidence includes correlational studies and 2 meta-analyses. Relevant outcomes are overall survival (OS), quality of life, and hospitalization. Most of the evidence is from reanalysis of existing randomized controlled trials (RCTs) 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 an 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 the 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 studies on the Presage ST2 Assay. Relevant outcomes are OS, 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.

For individuals who have heart transplantation who receive myTAI$_{HEART}$ 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% NPV 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 myTAI$_{HEART}$ 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.

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 negative predictive value (NPV) of the breath test the study evaluated (97.2%) was similar to endomyocardial biopsy (96.7%) and the sensitivity of the breath test (78.6%) was better than that for biopsy (42.4%). However, the breath test had 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 gene expression profiling (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 10 or fewer cases of rejection; therefore, performance data may be imprecise. Moreover, the PPV in CARGO II was only 4.0% for patients who were at least 2 to 6 months 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 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.

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.

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 (CLAD). 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.

SUPPLEMENTAL INFORMATION

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 2017, the American College of Cardiology Foundation, American Heart Association, and Heart Failure Society published a focused update of their 2013 guideline on the management of heart failure.[1,78,] Part of the focus of the update was on biomarkers. The guidelines stated that soluble suppression of tumorigenicity-2 (sST2) is a biomarker for myocardial fibrosis that may predict hospitalization and death in patients with heart failure and provides additive prognostic information to natriuretic peptide levels. The guidelines were based on a class IIb recommendation (weak; benefit ≥ risk) with level B-NR evidence (moderate-quality, nonrandomized) for the use of ST2 as an option to provide additive prognostic information to established clinical evaluation and biomarkers. The guidelines did not address other uses of ST2 or myTAI$_{HEART}$.

International Society of Heart and Lung Transplantation

In 2010, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients.[79,] The guidelines included the following recommendations (see Table 4).

Table 4. Guidelines for Postoperative Care of Heart Transplant Recipients

Recommendation	COR	LOE
"The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 postoperative months for surveillance of HT rejection."	IIa	C
"After the first post-operative year, EMB surveillance for an extended period of time (eg, every 4-6 months) is recommended in HT patients at higher risk for late acute rejection...."	IIa	C
"Gene Expression Profiling (AlloMap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT."	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.[80,] 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.[81,] 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, myTAI$_{HEART,}$ and the Presage ST2 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2012	New policy	
June 2013	Replace policy	Policy updated with literature review through March 5, 2015. References 2-3 and 12 added. Policy statements unchanged.
June 2014	Replace policy	Policy updated with literature review through March 4, 2014; reference 9 added. Policy statements unchanged.
June 2015	Replace policy	Policy updated with literature review, References removed and renumbered. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through August 28, 2017; no references added; reference 2 updated. In first policy statement, "grade 3" changed to "grade 2R/grade 3" due to updated ISHLT rejection grades and brand name of test removed; intent of statements unchanged. Policy statement corrected from "not medically necessary" to "investigational".
December 2018	Replace policy	Policy updated with literature review through August 22, 2018; references 5-9, 18, 20, and 22 added. 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.
December 2019	Replace policy	Policy updated with literature review through August 5, 2019; no references added. Policy statements unchanged.
December 2020	Replace Policy	Policy updated with literature review through August 25, 2020. references added. Content from policy 2.04.130 (Molecular Testing for Chronic Heart Failure and Heart Transplant) was merged into this policy and the title was changed to "Laboratory Tests Post Transplant and for Heart Failure".
December 2021	Replace Policy	Policy updated with literature review through October 20, 2021; references added. New investigational policy statement regarding dd-cfDNA testing in lung transplantation was added. Investigational policy statement for GEP testing (ie, AlloMap) in heart transplantation was updated to include use alone or in combination with dd-cfDNA testing (ie, HeartCare).
March 2022	Replace policy	Administrative formatting.