MEDICAL POLICY

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Medical Policy Title	**Laboratory Testing for Transplantation Rejection**
Policy Number	**2.02.55**
Current Effective Date	**July 17, 2025**
Next Review Date	**July 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Gene expression profiling (GEP) (i.e., AlloMap) is considered **medically appropriate** for the management of individuals after heart transplantation when **ALL** of the following criteria are met:

   A. The individual is age 15 years or older;

   B. The individual is 55 days to five (5) years post-heart transplantation;

   C. Heart allograft function is stable as demonstrated by **ALL** of the following:

      1. absence of signs or symptoms of congestive heart failure;

      2. current echocardiogram with left ventricular ejection fraction (LVEF) ≥ 45%;

      3. absence of severe cardiac allograft vasculopathy;

      4. no more than one (1) episode of moderate or severe (grade 3A [2R]) cellular rejection within the past year; **and**

      5. no history or evidence of antibody mediated rejection with associated hemodynamic compromise.

II. Measurement of donor-derived cell-free DNA (dd-cfDNA) (e.g., AlloSure, myTAIHEART, Prospera, Viracor TRAC, Clarava, Tuteva) is considered **investigational** for the management of individuals after organ transplantation including, but not limited to, the detection of acute transplant rejection or transplant graft dysfunction.

III. Measurement of donor and third party-induced CD154+T-cytotoxic memory cells (e.g., Pleximark) is considered **investigational** for the management of individuals after organ transplantation including, but not limited to, the detection of acute transplant rejection or transplant graft dysfunction.

IV. The Heart Molecular Microscope Diagnostic System (MMDx-Heart), and the Kidney Molecular Microscope Diagnostic System (MMDx-Kidney) are considered **investigational** for the management of individuals after organ transplantation including, but not limited to, the detection of acute transplant rejection or transplant graft dysfunction.

RELATED POLICIES

Corporate Medical Policy

7.02.04 Kidney Transplantation

7.02.06 Heart and Heart/Lung Transplant

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

Not Applicable

DESCRIPTION

Diagnosis of allograft rejection continues to rely on clinical monitoring and histologic confirmation by tissue biopsy. The current standard for identifying rejection after heart transplantation is endomyocardial biopsy (EMB). Using the International Society for Heart and Lung Transplantation (ISHLT) grading system, EMB samples can be classified as no rejection (Grade 0R), mild rejection (Grade 1R), moderate rejection (Grade 2R) or severe rejection (Grade 3R). These classifications help to establish and maintain the management of individuals following transplantation. Surveillance EMBs are necessary because rejection may not manifest any clinical signs or symptoms. EMBs are initially performed weekly and then at decreasing intervals. Although surveillance protocols vary among transplant centers, typically EMBs are performed weekly for the first six weeks, biweekly until the third month, monthly to six months and then every one to three months, as indicated. At 12 to 24 months following transplantation, EMBs may be performed every three to twelve months thereafter, the frequency is center dependent.

EMB are required whenever clinical signs of rejection emerge. However, the procedure is not without limitations. It is painful, invasive and does not detect rejection until it is actually present. Biopsy specimens may be difficult to obtain and/or inadequate due to poor venous access. Tissue samples may also be obscured by scarring. Reported complications of EMB include hematoma, infection, arrhythmia, ventricular perforation, and fistulas. EMB are reported to be limited by suboptimal interobserver reproducibility and uniform interpretation, and there may be a lack of histological findings in individuals who are hemodynamic compromise. Due to these limitations of tissue biopsy (i.e., a high degree of interobserver variability in the grading of results and its potential complications), less invasive alternatives have been investigated.

Surveillance of transplant kidney function relies on routine monitoring of serum creatinine, urine protein levels, and urinalysis. Allograft dysfunction may 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.

Allomap (CareDx, Inc., Brisbane, CA) 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 lower the score, the less the likelihood that the individual will experience rejection.

AlloSure Kidney (CareDx, Inc., Brisbane, CA) is a commercially available, next-generation sequencing assay that quantifies the fraction of dd-cfDNA in renal transplant recipients relative to total cell-free DNA by measuring 266 single nucleotide variants. Separate genotyping of the donor or recipient is not required, but individuals 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.

Prospera (Natera, Inc., San Carlos, CA) is a single nucleotide polymorphism (SNP)-based dd-cfDNA assay used for the detection of allograft rejection/injury in renal transplant individuals.

Pleximark is a novel assay, proprietary to Plexison, intended to assess the likelihood of rejection after renal transplantation by measuring T-cytotoxic memory lymphocytes to identify whether the transplanted kidney is eliciting an increased immune response from the transplant recipient, signifying kidney transplant rejection.

Molecular Microscope MMDx-Heart (Kashi Clinical Laboratories, Portland, OR) is a microarray-based system that utilizes microRNA profiling (mRNA gene expression analysis) to assess EMB specimens following heart transplantation. It is proposed for use in prognostic evaluations for AMR. The Kidney Molecular Microscope Diagnostic System (MMDx-Kidney) is an mRNA gene expression analysis of 1,494 genes utilizing microarray. It measures mRNA transcript levels in transplant kidney biopsy tissue, with allograft rejection and injury algorithm reported as a probability score.

Clarava (Verici Dx, Franklin, TN) is a pre-transplant prognosis test for the risk of early acute rejection. Tutivia (Verici Dx) is a post-transplant test focused upon acute cellular rejection, including sub-clinical rejection as correlates to histopathology findings. They are both blood tests using mRNA expression assay technology to produce a risk score for organ rejection with a proprietary AI algorithm. Tutivia used to be named Tuteva until a name change by Verici Dx in 2022.

SUPPORTIVE LITERATURE

In 2023, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients (Velleca 2023). EMBs remain the gold standard for monitoring rejection in the early post-transplant phase and in symptomatic individuals (Class IIa, Level of Evidence: C). More recently, the assessment of gene expression within allograft tissue and the identification of rejection-associated gene transcripts (e.g., Molecular Microscope, MMDx) has permitted improved discrimination between T-cell mediated or antibody mediated rejection and tissue injury, but this technology may not be clinically available outside of North America and is currently not in widespread use as a routine diagnostic test (No recommendation given). Since significant limitations associated with this invasive procedure have been recognized, many attempts have been carried out to identify

non-invasive procedures to decrease or eliminate the use of surveillance EMBs. For the non-invasive monitoring of acute heart transplant rejection, a Class IIa recommendation was made for Gene Expression Profiling (GEP) (i.e., Allomap) of peripheral blood can be used in low-risk individuals between two months and five 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 Class IIa, Level of Evidence: B. No other tests were recommended with the guideline update.

AlloMap (CareDx, Inc., Brisbane, CA)

Deng and colleagues (2006) reported results from the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study which included eight U.S. cardiac transplant centers. The study was conducted in three phases: 1) candidate gene discovery, 2) diagnostic development using polymerase chain reaction (PCR) assays and statistical methods, and 3) validation through a prospective, blinded study. A total of 281 CARGO samples from 166 patients, one or more years post-transplant consisting of 160 (56.9%) grade 0, 68 (24.1%) grade 1A, 23 (8.1%) grade 1B, 21 (7.4%) grade 2 and 9 (3.2%) grade 3A or higher were tested. At a cutoff of 30, the positive predictive value (PPV) was 6.8%, the negative predictive value (NPV) was 99.6%, and 68% of the tests were estimated to be below this value. Limitations of the study include the inability of the test to rule-out episodes of mild rejection found on biopsy and a low PPV relative to biopsy resulting in a full workup when a non-quiescent score is produced. The authors concluded that gene expression testing of blood cells can detect the absence of moderate/severe rejection, thus avoiding biopsy in certain clinical settings, but additional clinical experience is necessary to conclusively establish the predictive capacity of molecular testing for clinical events and its utility for monitoring immunosuppression.

Pham and colleagues (2010) conducted the Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial to test the hypothesis that a strategy of monitoring for rejection involving gene-expression profiling is not inferior to a strategy that involves routine biopsies, with respect to a composite outcome of rejection with hemodynamic compromise, graft dysfunction, death, or re-transplantation. The IMAGE study was a randomized, event-driven, industry-sponsored, noninferiority trial conducted at 13 U.S. cardiac transplantation centers from January 2005 through October 2009. Patients were required to be at least six months post-cardiac transplantation, clinically stable, and to have a left ventricular ejection fraction of 45% or greater. Exclusion criteria included a history of severe allograft vasculopathy, antibody-mediated rejection, or the presence of signs or symptoms of heart failure. Patients were randomly assigned 1:1 to either gene-expression profiling (gene-profiling group) or to routine endomyocardial biopsies (biopsy group). All patients underwent routine surveillance visits at pre-specified time intervals between three to 12 months based on the transplant center protocol. A GEP score of less than 34 was considered to be at very low risk for moderate/severe acute cellular rejection (ACR) and these patients were treated as if they had no evidence of rejection. A GEP score of 34 or higher returned for EMB within five days after the initial clinic visit and were managed according to the EMB result. Patients were followed for a maximum of 24 months, until they died, or until the study completion date, whichever occurred first. The primary outcome was the first occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or re-transplantation. Secondary outcomes included death from any cause, the number of biopsies performed, and biopsy-related complications. Of the 2,946 potentially eligible

patients, 1,665 (57%) were not approached or did not meet eligibility criteria. Although the reason was not recorded, common reasons for not enrolling a patient included a complicated medical course and preference of the treating physician to continue with biopsy-based monitoring. Of the 1,281 patients invited to participate, a total of 602 patients were randomly assigned to either GEP or routine EMBs. The median duration of follow-up after randomization was 19.0 months. Results showed the two-year rate of the composite primary outcome in the gene-profiling group was similar to the rate in the biopsy group (14.5% and 15.3%, respectively) with a hazard ratio of 1.04. The two-year cumulative rate of death was 6.3% in the gene-profiling group and 5.5% in the biopsy group. A total of 409 biopsies were performed in the gene-profiling group, as compared with 1,249 performed in the biopsy group. Of the 34 treated episodes of rejection in the GEP group, six were initially detected based on a biopsy due to an elevated GEP score. The other episodes were detected because of the presence of overt symptoms of heart failure or echocardiographic evidence of graft dysfunction. Of the 47 treated episodes in the biopsy group, 22 were asymptomatic and detected on routine-biopsy alone. The authors discussed that although gene-expression profiling may not have detected all the cases of asymptomatic rejection, not all asymptomatic episodes of rejection that occur more than six months after transplantation warrant treatment. Limitations include the fact that only 20% of potentially eligible patients were enrolled, presumably in many cases because the patient's own physicians chose not to include higher-risk candidates which biased the study toward inclusion of low-risk patients. Only 15% of the total included patients (n=87) had undergone transplantation between six months to one year prior which is considered the time period for the highest risk for rejection. There was a lack of blinding in the study, as well as a lack of uniformity in study protocol as each institution followed its own interval protocol for surveillance testing. There was a wide noninferiority margin resulting in a wide confidence interval with the possibility of a 68% increase in risk with the GEP strategy. The authors state the study had limited power to allow for a firm conclusion to be reached regarding the use of gene-expression profiling as a substitute for the performance of biopsies and called for a larger trial with a narrower noninferiority margin and longer follow-up.

Kobashigawa and colleagues (2015) conducted the Early Invasive Monitoring Attenuation through Gene Expression (EIMAGE) study, a single-center, randomized trial that compared the safety and efficacy of GEP with EMB in the monitoring of cardiac transplant rejection beginning 55 days to six months post-transplant. A total of 60 heart transplant patients meeting inclusion criteria were randomized to either GEP or EMB arms with monitoring at prespecified intervals of 55 days and three, four, five, six, eight, ten- and 12-months post-transplant. Endomyocardial biopsy outside of the scheduled visits was obtained in either group if there was clinical or echocardiographic evidence of graft dysfunction and for the GEP group if the score was above the specified threshold. A positive GEP of 30 or more between two and six months, or 34 or more after six months, prompted a follow-up biopsy. The primary end point included a composite of death/retransplant, rejection with hemodynamic compromise or graft dysfunction at 18 months post-transplant. A coprimary endpoint included change in first-year maximal intimal thickness by intravascular ultrasound, a recognized surrogate for long-term outcome. Results showed the composite end point was similar between the GEP and EMB groups (10% versus 17%; log-rank P=0.44). The coprimary end point of first-year intravascular ultrasound change demonstrated no difference in mean maximal intimal thickness

(0.35±0.36 versus 0.36±0.26 mm; P=0.944). The number of biopsy-proven rejection episodes (International Society for Heart and Lung Transplantation grading system ≥2R) within the first 18 months did not differ significantly between groups (three in the GEP group vs. one in the biopsy group; p=0.31). Of the rejections in the GEP group, one was detected after an elevated routine GEP test, while two were detected after patients presented with hemodynamic compromise. At one year, the SF-12 mental-health and physical-health summary scores were not significantly different between the two study arms. Limitations include the study was not powered, a small sample size, few primary composite end points were reached (eight patients). The authors concluded that GEP starting at 55 days post-transplant seemed comparable with EMB for rejection surveillance in selected heart transplant patients and did not result in increased adverse outcomes.

Crespo-Leiro and colleagues (2016) reported results of the CARGO II study, a prospective, observational, multi-center study with blood samples and associated clinical data collected from follow-up visits of cardiac transplantation recipients from May 2005 through February 2009. The study was designed to evaluate GEP in a different population from CARGO, patients two to six months post-transplantation and patient greater than six months post-transplantation. At a GEP cutoff of 34, for patients who were at least two to six months post-transplant, the sensitivity of GEP for detecting grade 2R/>3A was 25.0%, and the specificity was 88.7%. The PPV and NPV were 4.0% and 98.4%, respectively. Using the same cutoff of 34, for patients more than six months posttransplant, the sensitivity of GEP was 25.0%, the specificity was 88.8%, the PPV was 4.3%, and the NPV was 98.3%. The number of true positives used in the above calculations was five (9.1%) of 55 for patients at least two to six months post-transplant and six (10.2%) of 59 for patients more than six months post-transplant.

AlloSure-Heart (CareDx, Inc., Brisbane, CA)

Khush and colleagues (2019) reported the results of Donor-Derived Cell-Free DNA-Outcomes AlloMap Registry (D-OAR) study, a large, prospective, multi-center, clinical validation study which assessed the ability of a standardized dd-cfDNA assay to detect acute rejection (AR) in HT recipients. The primary objective was to determine whether the dd-cfDNA level in an HT recipient's blood can differentiate rejection from the absence of rejection, as determined by endomyocardial biopsy interpretation. Secondary outcomes were to determine whether graft dysfunction in the absence of rejection is associated with increased dd-cfDNA levels and to characterize dd-cfDNA levels in stable patients who have no evidence of AR. A total of 740 HT recipients from 26 centers and 33 patients at high risk for antibody mediated rejection (AMR) were included. The dd-cfDNA levels were correlated to paired events of biopsy-based diagnosis of rejection. Results showed the median dd-cfDNA was 0.07% in reference HT recipients (2164 samples) and 0.17% in samples classified as acute rejection (35 samples; P = 0.005). At a 0.2% threshold, dd-cfDNA had an 80% specificity, 44% sensitivity to detect rejection, a 97% NPV, and an 8.9% PPV.

AlloSure-Kidney (CareDx, Inc., Brisbane, CA)

Bloom and colleagues (2017) reported results from the Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) study, a multicenter study of renal allograft recipients using AlloSure. A total of 102 kidney recipients between one to three months post-transplantation were included in the analysis as they had undergone biopsy. From

these participants, 107 clinically indicated biopsies were compared to plasma dd-cfDNA. Biopsies performed for surveillance (n=34 biopsies) were excluded from analysis in this study, as only one biopsy for surveillance demonstrated acute rejection. There were 27 biopsy specimens from 27 patients with active rejection and 80 biopsy specimens from 75 patients without active rejection. With a cutoff of 1.0%, dd-cfDNA had an 85% specificity (95% CI, 79% to 91%) and 59% sensitivity (95% CI, 44% to 74%) to discriminate active rejection from no rejection. Positive and negative predictive values for active rejection at a cutoff of 1.0% dd-cfDNA were 61% and 84%, respectively. Limitations include the inability to estimate the performance of dd-cfDNA to discriminate active rejection in patients who may have had sub-clinical rejection because there were only 34 surveillance biopsies and only one finding of active rejection. Biopsy-matched blood samples were not collected for all biopsy specimens, and some of the matched blood samples were excluded due to issues, such as inadequate amount of total DNA or timing of the blood draw relative to the biopsy. Of all collected blood samples, 4.5 % did not render results due to some aspect of sample collection or testing.

Huang and colleagues (2019) reported early results of a single-center study using dd-cfDNA to determine rejection in kidney transplant recipients, particularly for the diagnosis of antibody-mediated rejection (ABMR) among patients with DSA. A total of 63 adult kidney transplant recipients with suspicion of rejection with dd-cfDNA and allograft biopsy were included. Of these, 27 (43%) patients had donor–specific antibodies and 34 (54%) were found to have rejection by biopsy: 10 (15.9%) were cell-mediated only, 22 (25.4%) were antibody-mediated only, and 2 (3.2%) were mixed cell-mediated and antibody-mediated. The percentage of dd-cfDNA was higher among patients with antibody–mediated rejection (ABMR; median 1.35%; interquartile range [IQR]: 1.10%-1.90%) compared to those with no rejection (median 0.38%, IQR: 0.26%-1.10%; P < .001) and cell–mediated rejection (CMR; median: 0.27%, IQR: 0.19%-1.30%; P = .01). The dd-cfDNA test did not discriminate patients with CMR from those without rejection. The area under the ROC curve (AUC) for CMR was 0.42 (95% CI: 0.17-0.66). For ABMR, the AUC was 0.82 (95% CI: 0.71-0.93) and a dd-cfDNA =0.74% yielded a sensitivity of 100%, specificity 71.8%, PPV 68.6%, and NPV 100%. For any rejection diagnosis (including either CMR, ABMR, or mixed rejection), the optimal cut point was a dd-cfDNA threshold of =0.74%, which was associated with a sensitivity of 79.4% and specificity of 72.4%. The associated PPV and NPV at the 0.74% threshold was 77.1% and 75.0%, respectively. At a dd-cfDNA threshold >1.0%, the sensitivity was 67.6%, specificity 72.4%, PPV 74.2%, and NPV 65.6%. The authors found dd-cfDNA was not able to discriminate CMR from no rejection. Limitations include the single-center design and small number of patients.

Martuszewski et al (2021) conducted a systematic literature review to evaluate the utility of donor derivative cell free DNA (dd-cfDNA) as a noninvasive biomarker for detecting allograft injury and acute rejection in kidney transplant recipients. The study aimed to assess the diagnostic performance of dd-cfDNA and its potential role in improving early detection, monitoring, and management of transplant outcomes. Inclusion criteria consisted of prospective and retrospective clinical trials evaluating dd-cfDNA in kidney transplantation. The results show that elevated dd-cfDNA levels were consistently associated with acute rejection often detectable before traditional markers like creatinine rise. dd-cfDNA threshold > 1% was often indicative of active rejection. Some studies identify a cutoff of 0.88%, correlating with biopsy confirmed rejection. dd-cfDNA shows similar or higher diagnostic accuracy than biopsies in some studies. Noninvasive real time monitoring was possible through blood

or urine samples. Limitations include false positive occurring due to concurrent infections or cancer, and T-Cell mediated rejection (TCMR) may not consistently elevate the dd-cfDNA. Researchers concluded that although data support its clinical utility for identifying antibodies mediated rejection (ABMR) more multi-center clinical trials are needed to establish standardized threshold, refined detection methods, and validate its effectiveness across diverse patient populations.

Prospera (Natera, Inc., San Carlos, CA)

Sigdel and colleagues (2018) reported results of a retrospective analysis which examined a novel single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) methodology to measure dd-cfDNA in various types of renal transplant recipients for the detection of allograft rejection/injury. A total of 277 plasma samples from 178 unique kidney transplant recipients were included in the analysis. Of these, 217 were biopsy-matched with 38 with active rejection (AR), 72 borderline rejections (BL), 82 with stable allografts (STA), and 25 with other injury (OI)). The 60 plasma samples with no matched biopsy were excluded. The SNP-based dd-cfDNA assay discriminated active from non-rejection status with an area under the curve (AUC) of 0.87, 88.7% sensitivity (95% CI, 77.7–99.8%) and 72.6% specificity (95% CI, 65.4–79.8%) at a prespecified cutoff (>1% dd-cfDNA). Based on a 25% prevalence of rejection in an at-risk population, the positive predictive value (PPV) was projected to be 52.0% (95% CI, 44.7–59.2%) and the negative predictive value (NPV) was projected to be 95.1% (95% CI, 90.5–99.7%).

For GEP to assess cardiac allograft rejection, one large RCT (IMAGE) compared GEP with EMB and found GEP to be noninferior. The evidence is sufficient to determine improvement in health outcomes.

For dd-cfDNA, most of the studies have limited methodological quality. All studies were retrospective or prospective cohorts, and many selected patients based upon clinical manifestation of graft injury. The gold standard test (biopsy) was often only applied in patients with clinical evidence of graft dysfunction which leads to questions around the clinical utility of dd-cfDNA as it is uncertain if it can detect subclinical graft injury. Validation studies are needed for the determined dd-cfDNA threshold, as well as the impact of prospective monitoring on clinical outcomes. It has been suggested that regular monitoring of dd-cfDNA may help to detect subclinical rejection, however, the optimum interval for dd-cfDNA measurement for routine transplant monitoring is still uncertain. Studies used minimum intervals of one month between tests, with shorter intervals in the early post-transplant period when the risk of rejection and infection are highest. Since normal levels do not rule-out CMR, clinically indicated biopsies should not be precluded by below threshold dd-cfDNA. More data are needed, particularly randomized trials comparing dd-cfDNA to the current standard of care.

For other tests for detection of transplant rejection including, allospecific CD154+T-cytotoxic memory cells and microarray-based systems tests, the evidence is insufficient to determine improvement in health outcomes.

PROFESSIONAL GUIDELINE(S)

The International Society for Heart and Lung transplantation (ISHLT) published updated comprehensive guidelines for the care of heart transplantation recipients building on their 2010

guidance. The 2023 update incorporates new evidence, expanded pediatric considerations, and detailed clinical recommendations across the transplant continuum. Four Task Force teams organize the guidelines each focusing on the keys phase or domain of the heart transplantation. The following are some Class I recommendations:

- During the pre-transplant optimization phase frailty should be assessed using the standard tool like the modified Fried criteria.
- A multidimensional nutritional assessment tool should be used to screen for malnutrition or risk thereof.
- Long term mechanical circulatory support is recommended in patients with high-risk features such as inotrope dependency or reversible contraindication.
- In pediatric patients, extracorporeal membrane oxygenation (ECMO) should be used as a bridge to transplant in cases of refractory heart failure.
- Asymptomatic moderate to severe rejection should prompt adjustments of maintenance immunosuppressive therapy.
- Donor hearts with ischemic time greater than 4 hours should only be used under specific favorable conditions.
- All transplant patients should be screened for alcohol tobacco and illicit drug use.
- Live vaccines are contraindicated post-transplant.

In 2023, the American Society of Transplant Surgeons (ASTS) supports consideration of donor-derived cell-free DNA (dd-cfDNA), as in AlloSure Kidney, for surveillance in kidney transplant recipients to exclude subclinical antibody mediated rejection (ABMR). Available from: asts-statement-on-donor-derived-cell-free-dna-(dd-cfdna)---updated-oct.-2024.pdf [accessed 2025 Jun 17]

- Recommends dd-cfDNA (AlloSure Kidney) for use in kidney transplant recipients experiencing acute allograft dysfunction to exclude rejection, particularly ABMR.
- Recommends that dd-cfDNA (AlloSure Heart) may be utilized to rule out subclinical rejection in heart transplant recipients.
- Recommends peripheral blood gene expression profiling (GEP), as in AlloMap Heart, 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.

REGULATORY STATUS

The United States Food and Drug Administration (FDA) regulates vaccines, blood and blood products, and biologics via the Center for Biologics Evaluation and Research (CBER) which ensures the safety, efficacy, and quality of these products. Refer to the FDA vaccines/blood/biologics website. Available from: https://www.fda.gov/vaccines-blood-biologics [accessed 2025 Jun 16]

The FDA maintains information for consumers and health professionals on vaccine, blood and biologics warnings and other safety information. Available from: Recalls (Biologics) | FDA [accessed 2025 Jun 16]

All AlloMap testing is performed at the CareDx reference laboratory in California. The test received United States Food and Drug Administration (FDA) 510(k) clearance in 2008 for use in conjunction with clinical assessment for aid 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 two months post-transplant.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81479 (E/I)	Unlisted molecular pathology procedure
81560 (E/I)	Transplantation medicine (allograft rejection, pediatric liver, and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
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
0018M (E/I)	Transplantation medicine (allograft rejection, renal), measurement of donor and third party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score (e.g., Pleximark)
0055U (E/I)	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma (myTAIHEART, TAI Diagnostics, Inc)
0087U (E/I)	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score (Molecular Microscope MMDx—Heart, Kashi Clinical Laboratories)
0088U (E/I)	Transplantation medicine (kidney allograft rejection) microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a

Code	Description
	probability score for rejection (Molecular Microscope MMDx—Kidney, Kashi Clinical Laboratories)
0118U (E/I)	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 (Viracor TRAC dd-cfDNA, Viracor Eurofins)
0319U (E/I)	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection (Clarava, Verici Dx, Verici Dx, Inc)
0320U (E/I)	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection (Tuteva, Verici Dx, Verici Dx, Inc)
0493U (E/I)	Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA (effective 10/01/24)
0508U (E/I)	Transplantation medicine, quantification of donor-derived cell-free DNA using 40 single-nucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cell-free DNA with risk for active rejection (effective 10/01/24)
0509U (E/I)	Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection (effective 10/01/24)
0540U (E/I)	Transplantation medicine, quantification of donor derived cell free DNA using next generation sequencing analysis of plasma, reported as percentage of donor derived cell free DNA to determine probability of rejection
0542U (E/I)	Nephrology (renal transplant), urine, nuclear magnetic resonance (NMR) spectroscopy measurement of 84 urinary metabolites, combined with patient data, quantification of BK virus (human polyomavirus 1) using real time PCR and serum creatinine, algorithm reported as a probability score for allograft injury status
0544U (E/I)	Nephrology (transplant monitoring), 48 variants by digital PCR, using cell free DNA from plasma, donor derived cell free DNA, percentage reported as risk for rejection
0576U (E/I)	Transplant medicine, liver, quantitative donor-derived cell-free DNA (dd-cfDNA) (effective 10/01/25)

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
T86.10 - T86.19	Complications of kidney transplant (code range)
T86.20 - T86.298	Complications of heart transplant (code range)
Z48.21	Encounter for aftercare following heart transplant
Z48.22	Encounter for aftercare following kidney transplant
Z94.0	Kidney transplant status
Z94.1	Heart transplant status

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Molecular Pathology Procedures (LCD L35000) [accessed 2025 Jun 17]

Billing and Coding: Molecular Pathology Procedures (LCA A56199) [accessed 2025 Jun 17]

Based upon our review, AlloSure, myTAIHEART, Prospera, Viracor TRAC, Clarava, Tutivia, Pleximark, MMDx-Heart, or MMDx-Kidney are not addressed in National or Regional Medicare coverage determinations or policies.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev. 121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service:

In some instances, one Medicare A/B MAC processes all the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service.

https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326 [accessed 2025 Jun 17]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
09/16/21, 07/21/22, 07/20/23, 07/18/24, 07/17/25	
Date	**Summary of Changes**
10/01/25	• Policy code edit to add CPT code 0576U (E/I) Transplant medicine, liver, quantitative donor-derived cell-free DNA (dd-cfDNA) (Effective 10/01/25).
07/17/25	• Annual review; policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
09/16/21	• Original effective date