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Corporate Medical Policy

Transplant Rejection Testing AHS – M2091

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Description of Procedure or Service

Transplant rejection involves an immune response to a transplanted organ. The recipient's immune system recognizes the donated organ as "foreign," thereby initiating an immune response as if the transplanted organ was a foreign antigen. This response may cause the organ transplant to fail (Vella, 2019). Gene expression profiling tests and serum cell-free DNA evaluation are possible ways to monitor organ transplant rejection (Carey et al., 2018; Crespo-Leiro et al., 2016; Gielis et al., 2015).

Related Policies
Immune Cell Function Assay for Organ Transplant Rejection AHS – G2098

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

Policy

BCBSNC may provide coverage for transplant rejection testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

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

When Transplant Rejection Testing is covered

The use of peripheral blood gene expression profiling tests (e.g., AlloMap) is considered medically necessary for the FDA-approved indication* (See Note) to aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection at the time of testing in conjunction with standard clinical assessment. Indicated for use in heart transplant recipients that are:

a. 15 years of age or older
b. At least 2 months (≥55 days) post transplant

Note: Peripheral blood gene expression profiling tests used must be FDA-approved for the use with heart transplant recipients.

When Transplant Rejection Testing is not covered

The use of donor-derived cell-free DNA (e.g., AlloSure) to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection is considered investigational.

The use of donor-derived cell free DNA tests for any other organ transplant, including but not limited to, lungs, liver, or heart is considered investigational.

The use of peripheral blood gene expression profiling tests for any other organ transplant not listed above, including but not limited to, kidney, lungs, or liver, is considered investigational.

The measurement of volatile organic compounds to assist in the detection of moderate grade 2R/grade 3 heart transplant rejection is considred investigational.

Policy Guidelines

Background

Solid organ transplant is a delicate process, requiring much oversight and evaluation of every party involved. Rejection, or failure of the transplant, is a potential outcome of any transplant case. At the molecular level, rejection is primarily caused by a component of the adaptive immune system, the major histocompatibility complex (MHC) proteins. These proteins must match between donor and recipient, or the transplant can fail (Vella, 2019).

The MHC proteins' primary function is acting as the platform on which T cells identify antigens. Typically, these MHC proteins bind foreign antigens, which are then recognized as such by T cells. From there, the T cells can generate an immune response to handle the antigen. However, the MHC protein products must be identified as "self" by these T cells as well. If an organ donor's MHC protein does not match the recipient's, the recipient's T cells may identify the MHC of the donated organ as "foreign" and subsequently implement an immune response. This eventually starts the cascade of events that causes the transplant to fail (Vella, 2019).

Numerous methods mitigate this immune response. Immunosuppressants, which cause desensitization of the immune response, and more have been proposed as methods to circumvent this immune response (Vella, 2019). Other methods involve evaluating the risk of rejection, such as AlloMap (from CareDx). "The AlloMap test is based on quantitative real-time polymerase chain reaction methodology (qRT-PCR) using RNA purified from peripheral blood mononuclear cells (PBMC)" (CareDX, 2019a). It is a gene expression test (11 informative genes, 9 control genes) that proposes 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" (FDA, 2008). Its FDA approval states that it is intended for heart transplant recipients, 15 years or older, and ≥55 days post-transplant (FDA, 2008).

Other gene expression profiles available for assessment of transplant rejection include Molecular Microscope (MMDx, 1283 genes for heart transplants, 1494 genes for kidney transplants). MMDx measures the mRNA levels of a set number of genes (depending on the organ), then compares those mRNA levels to a reference set of biopsies. Currently, MMDx has tests available for heart, kidney, lung, and liver transplant assessment (MMDx, 2020). TruGraf also offers a gene expression panel intended for kidney transplant patients. TruGraf proposes that it can identify if a patient is "immune activating" (potentially rejecting) or "immune quiescent" (stable), allowing a clinician to evaluate potential presymptomatic kidney damage without use of a biopsy (TruGraf, 2018).

Tissue gene expression is not the only medium tested for rejection. The use of cell-free DNA has shown much promise as a minimally invasive detection method for allograft rejection, and may be used to complement or, ultimately, replace tissue biopsies in the future (Pattar & Greenway, 2020). AlloSure, a test offered by the same parent company as AlloMap, evaluates cell-free DNA in the blood for kidney transplant patients. The test states that when graft injury occurs, donor-derived cell-free DNA is released into the blood where it can be measured as a marker of kidney transplant surveillance (CareDX, 2019b). Bloom et al. (2017) evaluated AlloSure with 102 kidney recipients, and they concluded that a donor-derived cell-free

DNA (dd-cfDNA) level of >1% indicated active rejection of the graft (Bloom et al., 2017). According to the manufacturer, AlloSure is validated for use at least 14 days post-transplant in individuals aged 18 years or older who have received a single kidney transplant (CareDX, 2019c).

Viracor Diagnostics offers dd-cfDNA assays for heart, kidney, and lung transplant recipients. Viracor's tests use next-generation sequencing (NGS) to monitor the percentage of dd-cfDNA in the recipient's plasma, which may help in diagnosis of rejection (Viracor, 2019). Similarly, Natera, a genetic testing company, has developed the Prospera test, which uses cell-free DNA to assess kidney transplant rejection. This blood test is now covered by Medicare for all kidney transplant recipients (Natera, 2020). Finally, myTAIHEART, from TAI diagnostics, measures cell-free DNA in a blood sample to assist in identifying "heart transplant recipients who have a low probability of moderate/severe acute cellular rejection" (TAI_Diagnostics, 2020).

Another medium used for assessment of rejection is breath. Heartsbreath is an FDA-approved test that purports to predict the probability of grade 3 rejection in heart transplant patients. The test detects "volatile organic compounds" (Messana, 2004). The FDA notes that this test does not replace biopsy and is only intended as an adjunct to biopsies. The breath markers are considered to be markers of "oxidative stress" (FDA, 2004).

Clinical Validity and Utility

Pham et al. (2010) conducted a randomized study comparing gene expression profiling and endomyocardial biopsies for monitoring heart transplant patients. A total of 602 patients who had undergone cardiac transplantation 6 months to 5 years previously were included. Both groups were found to have similar rates of primary outcomes, hazard ratios, and 2 year all-causes of mortality. Patients monitored with gene expression profiling underwent fewer biopsies. The researchers concluded that "Among selected patients who had received a cardiac transplant more than 6 months previously and who were at a low risk for rejection, a strategy of monitoring for rejection that involved gene-expression profiling, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies (Pham et al., 2010)."

Deng et al. (2014) evaluated the variability of a heart recipient's gene expression profiling test (AlloMap) scores. Variability was defined as the "the standard deviation of an individual's cumulative test scores." A total of 369 patients from the Invasive Monitoring Attenuation by Gene Expression Profiling (IMAGE) study were included, and "gene expression profiling score variability, but not ordinal scores or scores over threshold, was independently associated with future clinical events." The hazard ratio for a 1 unit increase in variability was found to be 1.76 (Deng et al., 2014).

Kobashigawa et al. (2015) conducted a single-center randomized controlled trial to evaluate gene expression profiling (GEP) versus endomyocardial biopsy (EMB) starting at 55 days post-transplant. Sixty heart transplant patients meeting inclusion criteria were randomized beginning at 55 days post-transplant to either GEP or EMB arms. A positive GEP ≥30 between 2 and 6 months, or ≥34 after 6 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. The researchers concluded that "GEP starting at 55 days post-transplant seems comparable with EMB for rejection surveillance in selected heart transplant patients and does not result in increased adverse outcomes. GEP also seems useful to guide corticosteroid weaning" (Kobashigawa et al., 2015).

M. G. Crespo-Leiro et al. (2015) assessed the "prognostic utility of within-patient variability of GEP scores in predicting future significant clinical events, the negative predictive value (NPV) and the positive predictive value (PPV) of GEP score variability in predicting future significant clinical events." A total of 737 patients from the Cardiac Allograft Rejection Gene Expression Observational (CARGO) II trial were included. Estimated prevalence of events was found to be 17%, and events occurred at a median of 391 days after the final GEP test. The authors found that "the GEP variability area under the receiver operator characteristics curve for the prediction of a composite event was 0.72. The NPV for GEP score variability of 0.6 was 97% and the PPV for GEP score variability of 1.5 was 35.4%." The authors concluded that "The

GEP score variability may be used in estimating the likelihood of events of death, re-transplantation or graft dysfunction occurring in patients beyond 315 days post-transplant" (M. G. Crespo-Leiro et al., 2015).

Furthermore, (Crespo-Leiro et al., 2016) validated the clinical performance of the gene-expression profiling technology in an independent patient population from the CARGO II study. A total of 399 patients were included. The GEP score ranged from 0-39, and the authors identified the optimal cut-off to be 34. At this score (at ≥6 months after transplant), "95.5% (381/399) of GEP tests were true negatives, 4.5% (18/399) were false negatives, 10.2% (6/59) were true positives, and 89.8% (53/59) were false positives." Based on 938 paired biopsies, the area under the curve for distinguishing ≥3A rejection was found to be 0.70 and 0.69 for 2-6 months and ≥6 months, respectively. The authors concluded, "[T]he choice of threshold score for practical use of GEP testing should consider overall clinical assessment of the patient's baseline risk for rejection" (Crespo-Leiro et al., 2016).

Fujita et al. (2017) followed up on the CARGO study by investigating the long-term mortality of 46 patients. They found that 23 patients had an increased AlloMap score 6-9 months after heart transplant whereas the remaining 23 patients had a decreased score. After a median follow-up time of 8.1 years, all-cause mortality was significantly elevated in patients with an AlloMap increase compared with patients with a decreased score. The authors concluded, "Dynamic changes of the AlloMap score between 6 and 9 months after HT [heart transplant] were strongly related to all-cause long-term survival after HT. These results suggest that AlloMap potentially displays a useful tool to estimate the patients' risk for long-term mortality (Fujita et al., 2017)."

Carey et al. (2018) analyzed 18 months of follow-up in a national cohort of 27 dual organ recipients (18 heart-kidney, 8 heart-liver, 1 heart-lung) matched to 54 heart-only recipients for gender, age, and time to first GEP (AlloMap) test. They found that "during the first 90 days post-transplant, the mean GEP score for dual organ recipients was 25.2 ± 9.1, vs. 23.5 ± 7.7 for heart-only recipients (P = 0.48), with final GEP scores being 29.1 ± 6.1 and 32.3 ± 3.4, respectively (P = 0.34). GEP scores increased over time at a similar rate (P = 0.33) for both groups. During follow-up, mean GEP score among patients with cytomegalovirus infection was 32.3 (n = 14), compared to 26.7 in patients without cytomegalovirus. Only 4 (2%) of 233 biopsies were positive for mild antibody-mediated rejection; all occurring in 2 heart-only recipients (GEP scores = 18-33)" (Carey et al., 2018).

Bakir et al. (2018) analyzed time-dependent phenomapping of clinical and molecular data sets from 94 heart transplant patients (1557 clinical encounters) in order to determine its accuracy in guiding clinical management. Phenomapping's associations were analyzed with "immunosuppression therapy, biomarkers, and the combined clinical end point of death, allograft loss, retransplantation, and rejection," and these findings were further correlated with "clinical parameters, human leucocyte (*sic*) antigen antibody titers, and peripheral blood mononuclear cell gene expression of the AlloMap test genes" (Bakir et al., 2018). The authors found that patients in the group with higher event rates had "increased human leukocyte antigen class I and II antibody titers, higher expression of the *FLT3* AlloMap gene, and lower expression of the *MARCH8* and *WDR40A* AlloMap genes." The authors concluded that "time-dependent precision phenotyping is a mechanistically insightful, data-driven approach to characterize patterns of clinical care and identify ways to improve clinical management and outcomes" (Bakir et al., 2018).

Phillips et al. (2004) evaluated another novel marker of heart transplant rejection: volatile organic compounds (VOCs). A total of 1061 samples were taken from 539 patients prior to endomyocardial biopsy. The combination of 9 VOCs in the algorithm "identified Grade 3 rejection (sensitivity 78.6%, specificity 62.4%, cross-validated sensitivity 59.5%, cross-validated specificity 58.8%, positive predictive value 5.6%, negative predictive value 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, positive predictive value 45.2% and negative predictive value 96.7% (Phillips et al., 2004)." The authors concluded that "a breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 heart transplant rejection than a biopsy reading by a site pathologist, but the negative predictive values of the 2 tests were similar" (Phillips et al., 2004). However, the Centers for Medicare and Medicaid (CMS) determined that the evidence does not adequately define the technical characteristics of the test nor demonstrate that Heartsbreath testing to predict heart transplant rejection improves health outcomes (CMS, 2008).

Agbor-Enoh et al. (2019) assessed the donor-derived cell-free DNA (ddcfDNA or dd-cfDNA) levels in 106 lung transplant patients and monitored them for development of allograft failure ("defined as severe chronic lung allograft dysfunction [CLAD], retransplantation, and/or death from respiratory failure"). The average level of donor-derived cell-free DNA (%ddcfDNA) was measured and correlated with allograft failure. The authors separated the patients into three tertiles, with median values of 3.6% in the highest tertile, 1.6% in the middle, and 0.7% in the lowest. The highest tertile was calculated to have a 6.6-fold higher risk of allograft failure compared to the lowest and middle tertiles. The researchers concluded, "[L]ung transplant patients with early unresolving allograft injury measured via %ddcfDNA are at risk of subsequent allograft injury, which is often clinically silent, and progresses to allograft failure" (Agbor-Enoh et al., 2019).

A 14-center post-transplant longitudinal study by Bromberg et al. (2017) published in *The Journal of Applied Laboratory Medicine* measured the dd-cfDNA at 1, 2, 3, 4, 6, 9, and 12 months post-transplant. A total of 380 blood samples were taken during the study, and the median dd-cfDNA value was 0.21%. A value of 1.20% is at the 97.5th percentile. The authors conclude, "In a renal transplant recipient, a dd-cfDNA level above 1.2% is out of range and potentially abnormal" (Bromberg et al., 2017).

Huang et al. (2019) evaluated the ability of cell-free DNA to detect rejection in kidney transplant patients. A total of 63 kidney transplant patients with suspicion of rejection were included. Twenty-seven of these had donor-specific antibodies, and 34 were considered to have rejection by biopsy. The percentage of donor-specific cell-free DNA (dd-cfDNA) was higher in patients with antibody-mediated rejection (AMR) compared to those with no rejection and cell-mediated rejection (AMR: 1.35%, no rejection: 0.38%, cell-mediated rejection: 0.27%). A dd-cfDNA percentage of 0.74% was found to yield a sensitivity of 100%, a specificity of 71.8%, a positive predictive value of 68.6%, and a negative predictive value of 100%. The authors concluded that "the dd-cfDNA test did not discriminate CMR from no rejection among kidney transplant recipients, although performance characteristics were stronger for the discrimination of [AMR]" (Huang et al., 2019).

Schutz et al. (2017) evaluated graft-derived cell-free DNA (GcfDNA)'s ability as a marker for liver transplant rejection. A total of 115 patients were included, and 17 patients contributed samples (n = 31) during a biopsy-proven rejection episode; the remaining 88 contributed samples (n = 282) during stable periods. The samples from the rejection cohort were found to have a higher percentage of GcfDNA than the stable cohort (29.3% vs 3.3%). Liver function tests (LFTs) had low correlation rates with GcfDNA, and the area under the curve was 97.1% for GcfDNA. Overall, the authors concluded that "in this study, determination of GcfDNA allowed for earlier and more sensitive discrimination of acute rejection in liver transplant patients as compared with conventional LFTs" (Schutz et al., 2017).

Grskovic et al. (2016) performed a validation of AlloSure. The authors included 1117 samples, and AlloSure was used to quantify the fraction of donor-derived cell-free DNA (dd-cfDNA) in both related and unrelated donor-recipient pairs. The quantifiable range was found to be linear from 0.2% to 16%, and the across-runs coefficient of variation was found to be 6.8%. The limit of blank was found to be 0.10%, limit of detection was 0.16%, and limit of quantification was 0.20%. The authors concluded that "application of the assay to clinical samples from heart transplant recipients demonstrated increased levels of dd-cfDNA in patients with biopsy-confirmed rejection and decreased levels of dd-cfDNA after successful rejection treatment" (Grskovic et al., 2016).

M. Crespo-Leiro et al. (2015) compared the levels of dd-cfDNA in heart transplant recipients with biopsy-confirmed rejection to recipients without rejection. A total of 151 plasma samples from 63 patients were evaluated, and 132 of these samples were biopsied. An AlloMap score was also taken. The dd-cfDNA levels were found to be higher in patients with rejection (1.7% vs 0.99%), and an area under curve (AUC) was measured to be 0.68. The mean AlloMap score was found to be 24.3 in non-rejection patients and 28.3 for rejection patients. The authors found that the dd-cfDNA levels and AlloMap score were not significantly correlated, proposing that these tests may be complementary. Combining the AlloMap and plasma dd-cfDNA levels yielded an AUC of 0.78 (M. Crespo-Leiro et al., 2015).

Jordan et al. (2018) investigated the use of dd-cfDNA alongside donor-specific antibodies (DSA) testing in identifying antibody-mediated rejection (AMR) of renal allograft recipients (n = 87 patients). They note that the median level of dd-cfDNA was 2.9% in DSA+ patients who have active AMR whereas the dd-cfDNA was significantly lower in both DSA+ patients without AMR (0.34%) or DSA- patients (0.29%). "The positive predictive value of dd-cfDNA (at 1%) to detect active ABMR in DSA+ patients was 81%, whereas the negative predictive value was 83%. The positive predictive value for DSA+ alone was 48%... The combined use of dd-cfDNA and DSA testing may improve the noninvasive diagnosis of active ABMR in kidney transplant patients. Patients with dd-cfDNA+/ DSA+ results have a high probability of active ABMR (Jordan et al., 2018)."

Gielis et al. (2020) obtained samples from 107 kidney transplant recipients to investigate the role of cell-free DNA in acute kidney rejection. Samples were collected between one day and three months after transplantation. The authors noted that increases in cell-free DNA "above a threshold value of 0.88% were significantly associated with the occurrence of episodes of acute rejection (P = 0.017), acute tubular necrosis (P = 0.011) and acute pyelonephritis (P = 0.032)" (Gielis et al., 2020). However, the authors also note that "Although increases in plasma ddcfDNA% are associated with graft injury, plasma ddcfDNA does not outperform the diagnostic capacity of the serum creatinine in the diagnosis of acute rejection" (Gielis et al., 2020).

Peabody et al. (2020) researched the clinical utility of the dd-cfDNA Prospera test by Natera to lower the rate of kidney graft loss. Simulated cases of 154 nephrologists were analyzed for this study; some physicians used dd-cfDNA testing and some did not. Results show that at baseline, there were no differences between primary diagnosis, biopsy decisions, or therapeutic management. However, after use of the cc-cfDNA test, "intervention nephrologists were more likely to arrive at the diagnosis of rejection (OR 4.00, 95% CI 1.93-8.30), make a correct decision on biopsy/transplant center referral (OR 11.07, 95% CI 4.87-25.16), and properly adjust therapeutic management (OR 2.37, 95% CI 1.07-5.24)" (Peabody et al., 2020).

Sigdel et al. evaluated an SNP-based assay's accuracy in identifying allograft rejection or injury. The assay is intended to identify rejection through measurement of donor-derived cell-free DNA (dd-cf DNA). A total of 193 unique renal transplant patients were included, with a total of 300 plasma samples provided. Of the 300 samples, 217 were biopsy-matched, 38 had active rejection (AR), 72 had borderline rejection (BL), 25 had other injury (OI), and 82 were stable (STA). The authors found that median dd-cfDNA was higher in biopsy-proven AR (2.3%) compared to BL (0.6%), OI (0.7%), and STA (0.4%). The assay was found to discriminate active rejection from non-rejection at an area under curve of 0.87, 88.7% sensitivity, and 72.6% specificity (at a cutoff of 1% dd-cfDNA). Of 13 patients with AR findings after 6 months, 12 tested positive by the assay. The authors concluded that their data supported the "feasibility of using this assay to detect disease prior to renal failure and optimize patient management in the case of allograft injury" (Sigdel et al., 2018).

Altug et al. performed an analytical validation of a "single-nucleotide polymorphism [SNP]-based donor-derived cell-free [cf] DNA assay for detecting rejection in kidney transplant patients". This test measured 13962 SNPs and was validated using 66 unique samples with 1064 replicates. The authors measured the cf-DNA fraction in related and unrelated (genetically related) donor-recipient pairs. The authors identified a "limit of blank" of 0.11% and a limit of detection and quantitation of 0.15% for unrelated donors. For related donors, a limit of blank of 0.23% and a limit of detection and quantitation of 0.29% was identified. Other metrics such as precision and linearity were found to be identical for both categories. The coefficient of variance was found to be 1.8%. The authors concluded that their findings were an adequate analytical validation of the assay (Altug et al., 2019).

Guidelines and Recommendations

International Society of Heart and Lung Transplantation (ISHLT) (Costanzo et al., 2010; ISHLT, 2016)

In 2010, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients (Costanzo et al., 2010). The guidelines included the following recommendations:

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

In a 2016 guideline discussing antibody-mediated rejection (AMR) of the lung, the ISHLT noted the lack of specific diagnostic criteria for AMR and listed allograft dysfunction, positive histology, positive C4d staining, and donor-specific anti–human leukocyte antigen (HLA) antibodies (DSA) as potential diagnostic items for AMR (ISHLT, 2016).

Heart Failure Association of the European Society of Cardiology (Crespo-Leiro et al., 2018)

The Heart Failure Association of the European Society of Cardiology published a position statement on Advanced Heart Failure (Crespo-Leiro et al., 2018) which states: "Post-transplant patients should undergo a pre-defined regimen of graft biopsies, titration of immunosuppressive and other therapies, rejection monitoring, assessment for infections, transplant coronary artery disease and/or cardiac allograft vasculopathy, immunosuppression side effects, and other potential complications including neoplasia, and co-morbidities that require comprehensive treatment."

European Association of Urology (EAU) (Rodriguez Faba et al., 2020)

The EAU published guidelines on renal transplantation. In it, they state that "the ultimate standard for the diagnosis of rejection is transplant biopsy, because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy (Rodriguez Faba et al., 2020)."

Renal Association (RA, 2017)

The RA published guidelines regarding post-operative care for kidney transplant patients. These guidelines have been endorsed by the British Transplant Society (BTS). The assessment of rejection recommendations are listed below:

- "We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient."

- "We recommend that a protocol transplant renal biopsy, defined as a biopsy performed in a stable graft without clinical evidence of acute rejection, be considered in the setting of persisting delayed graft function."

Furthermore, in the rationale, the RA states that "Rejection episodes are characteristically associated with loss of graft function but diagnosis is best established by a percutaneous biopsy since it differentiates rejection clearly from other causes of graft dysfunction" (RA, 2017).

American Association for the Study of Liver Diseases and the American Society of Transplantation (AASLD, AST, 2013)

These joint guidelines provide guidance on the long-term management of liver transplants. Their recommendations concerning assessment of rejection are as follows:

- "Rejection can be reliably diagnosed only on the basis of liver histology; a biopsy sample should be taken before treatment initiation and classified according to the Banff criteria."

- The guidelines also note that "Both forms of rejection are, until the late stages, asymptomatic, and the diagnosis is made through the investigation of abnormal liver tests; the diagnosis can be confirmed only on the basis of histology" (AASLD/AST, 2013).

Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO, 2010)

The KDIGO does not list any gene expression or cell-free DNA techniques in their guideline for managing transplant recipient patients (KDIGO, 2010).

Federal Regulations, as applicable

AlloMap was approved by the FDA on August 26, 2008 as an In Vitro Diagnostic Multivariate Index assay (IVDMIA) test service, performed in a single laboratory, assessing the gene expression profile of RNA isolated from peripheral blood mononuclear cells (PBMC). AlloMap Testing is intended 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. Searches for "rejection," "transplant rejection," and "transplant" on the FDA Device database on 08/03/2020 yielded no relevant results (FDA, 2020).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

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

Applicable service codes: *0055U, 0085T, 0087U, 0088U, 0118U, 81479, 81595, 81599, 86849, 0221U*

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

Scientific Background and Reference Sources

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Policy Implementation/Update Information

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

12/10/19 Policy archived. (jd)

For Policy titled Transplant Rejection Testing AHS – M2091

12/10/19 New Policy. BCBSNC will provide coverage for gene expression profiling testing for heart transplant rejection (e.g., AlloMap) when it is determined to be medically necessary because the criteria and guidelines are met. The use of donor-derived cell-free DNA tests (e.g., AlloSure) and measurement of volatile organic compounds are considered investigationl. Medical Director review 11/2019. (jd)

4/28/20 Specialty Matched Consultant Advisory Panel review 4/2020. Medical Director review 4/2020. (jd)

10/1/20 The following code was added to the Billing/Coding section effective 10/1/20: 0221U. (jd)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Policy guidelines and references updated. Medical Director review 10/2020. (jd)

5/4/21 Specialty Matched Consultant Advisory Panel review 4/2021. Medical Director review 4/2021. (jd)