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, measurement of volatile organic compounds and serum cell-free DNA evaluation are proposed ways to monitor organ transplant rejection as an alternative to invasive tissue biopsy (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
Transplant Rejection Testing AHS – M2091

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 considered investigational.

Policy Guidelines

Background

Solid organ transplant 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 and 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 perform 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, 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 it can “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 only has tests available for heart and kidney transplant assessment but is planning to offer tests for lung and liver transplant patients (MMDx, 2019). 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).

Gene expression is not the only medium tested for rejection. AlloSure, a test offered by the same parent company as AlloMap, evaluates cell-free DNA in the blood for kidney transplant patients. The tests 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 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). Similarly, 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).

Another medium used for assessment of rejection is breath. Heartbreath 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. There were 602 patients included who had undergone cardiac transplantation 6 months to 5 years previously. 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 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”. The IMAGE study included 369 patients, and “gene expression profiling score variability, but not ordinal scores or scores over the 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 researcher 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).”

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.” The Cardiac Allograft Rejection Gene Expression Observational (CARGO) II trial included 737 patients. 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, which included 399 patients. 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% (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 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 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”. 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).”

Philips et al evaluated another novel marker of heart transplant rejection, volatile organic compounds (VOCs). 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%”. 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, 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).

The evidence for individuals with a renal transplant and clinical suspicion of allograft rejection who receive testing of donor-derived cell-free DNA to assess renal allograft rejection includes diagnostic accuracy studies. Development of the AlloSure test was conducted in a multicenter prospective study Bloom et al. (2017), which examined the diagnostic performance of dd-cfDNA for detecting moderate-to-severe rejection; the negative predictive value 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Guidelines and Recommendations

International Society of Heart and Lung Transplantation (ISHLT)

In 2010, the International Society of Heart and Lung Transplantation issued guidelines for the care of heart transplant recipients which included the following:

- 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 low-risk patients between 6 months and 5 years post-transplant.

Heart Failure Association of the European Society of Cardiology

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, 2018)

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., 2018).”

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.”

Kidney Disease: Improving Global Outcomes (KDIGO, 2018)

KDIGO does not list any gene expression or cell-free DNA techniques in their guideline for managing transplant recipient patients (KDIGO, 2018).
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Federal Regulations, as applicable

AlloMap was approved by the FDA on August 26, 2008 as an In Vitro Diagnostic Multivariate Index assay (IVDIMA) 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 8/23/2019 yielded no relevant results (FDA, 2019).

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

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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CMS. (2008). National Coverage Determination (NCD) for Heartsbreath Test for Heart Transplant Rejection (260.10). Retrieved from https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCId=325&amp;amp;amp;ncdver=1&amp;amp;amp;SearchType=Advanced&amp;amp;amp;CoverageSelection=Both&amp;amp;amp;NCSelection=NCA%7cCAL%7cNCD%7cMEDC%7cTA%7cMCD &amp;amp;amp;ArticleType=Ed%7cKey%7cSAD%7cFAQ&amp;amp;amp;PolicyType=Final&amp;amp;amp;ss=%7c5%7c6%7c66%7c67%7c9%7c38%7c64%7c65%7c44&amp;amp;amp;KeyWord=transplant&amp;amp;amp;KeyWordLookUp=Doc&amp;amp;amp;KeyWordSearchType=Exact&amp;amp;amp;kq=true &amp;amp;amp;bc=IAAAAACAAAAAAA3d%3d&amp;amp;amp;:


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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)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.