Molecular Diagnostic Assays and Breath Testing for Transplant Rejection

Humana

Medicaid Medical Coverage Policy

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Description

A biopsy is considered the gold standard for the diagnosis of organ transplant rejection. Noninvasive methods for the detection and surveillance of transplant rejection have been developed with the goal of reducing the number of biopsies. These tests include, but may not be limited to, the following:

Antigen-Specific T-cell Function Assay
CD154+-T-cytotoxic memory cell testing has been developed to reportedly determine the likelihood of acute cellular rejection by measuring the immune response of recipient lymphocytes to donor or donor-like cells. The tests utilize an index ratio, which purportedly represents cell activity of the T-cytotoxic memory cells toward the donor cells and assesses the risk of rejection. This testing is designed for determining rejection risk in renal transplants (eg, Pleximark Tx) and for pediatric liver and small bowel transplants (eg, Pleximmune).

Blood Group Antigen Testing
Plays a role in recognizing foreign cells in the bloodstream. If a blood type mismatch occurs during a blood transfusion it could lead to an immune response and possible illness. RBC antigen genotyping assays have been proposed as an alternative approach to determining compatibility of donated blood. Blood group genotyping purportedly overcomes blood grouping limitations by looking directly into the DNA sequence and thereby avoiding any donor cell or antibody interference.

Breath Testing

Breath methylated alkane contour (BMAC) (eg, Heartsbreath) is a test that is purportedly indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection an individual who have received a heart transplant within the preceding year. It is intended to be used as an adjunct to, and not as a substitute for, an endomyocardial biopsy. The use of the test is limited to individuals who have had an endomyocardial biopsy within the previous month.[28] By breathing into a plastic mouthpiece that is attached to a breath collecting device, the amount of methylated alkanes in the individual's breath is supposedly subtracted from that found in the room. A value is then generated and is compared to the results of a biopsy performed during the previous month to measure the probability of the implanted heart being rejected.

Combined Gene Expression Profiling and Donor-Derived Cell-Free (dd-cfDNA) tests

These tests are designed to reportedly provide a broad assessment of immune quiescence (inactivity) and graft injury by combining a gene expression profiling test and a dd-cfDNA test (eg, OmniGraf).

dd-cfDNA

Biomarker blood tests purportedly determine allograft injury by measuring DNA fragments that are supposedly released into the bloodstream from the injured donor allograft cells. The goal of these tests is to predict active rejection using these measurements. These tests include, but may not be limited to:

- Viracor TRAC (heart, kidney, liver and lung)
- VitaGraft Kidney

Gene Expression Profiling

Immune response gene expression panel (eg, nCounter Human Organ Transplant Panel) has been developed to assess immune response following organ transplant utilizing a panel of 770 genes across 37 pathways that purportedly evaluates heart, kidney, liver and lung rejection.

Messenger deoxyribonucleic acid (mDNA) and Messenger ribonucleic acid (mRNA) gene expression utilize proprietary microarrays and algorithms based on a reference set of biopsies to provide scores to assess the probability of rejection by reportedly measuring cell-mediated rejection. The tests are purportedly utilized for heart, kidney and lung transplants. Examples of mDNA and mRNA gene expression assays include, but may not be limited to:

- Clarava pretransplant mRNA expression assay
- Molecular Microscope Diagnostic system (eg, MMDx Heart, MMDx Kidney, MMDx Lung)
- TruGraf blood gene expression test

Molecular gene expression assay (eg, Kidney Solid Organ Response Test [kSORT]) has been developed for kidney transplant rejection to reportedly detect individuals who are at high risk for acute rejection. Polymerase chain reaction (PCR) is utilized to measure the relative messenger ribonucleic acid (mRNA) expression levels of 17 genes that have been known to be associated with acute rejection. Individuals are classified into high, low or indeterminate risk according to a correlation-based algorithm.[21]

Human Leukocyte Antigen Testing

Human leukocyte antigen (HLA) testing is a process used to determine the compatibility between a donor and a recipient for organ or stem cell transplant. It assesses the HLA antigens present in the blood, which are crucial for the immune system's ability to recognize foreign tissues. The process involves blood tests to analyze the HLA antigens and helps identify suitable tissue donors, improving the chances of a successful transplant.

Urine-Based Tests for Allograft Rejection

Several urine-based tests have been proposed utilizing various biomarkers to aid in the diagnosis of acute rejection in kidney transplant recipients. Purportedly, the tests measure urine mRNA, urine proteins and/or urine proteomics. Some tests measure several biomarkers (eg, QiSant [also known as QSant**]**) to reportedly determine acute kidney transplant rejection. The biomarkers include, but may not be limited to, cfDNA, methylated cfDNA, clusterin, CXCL10, creatinine and total protein, which are integrated into an algorithm to supposedly determine kidney risk rejection scores.

Coverage Determination

There are no covered indications; refer to Coverage Limitations Section.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for any of the following:

- Antigen-specific T-cell function assays (eg, CD154+T-cytotoxic memory cells, Pleximark Tx [0018M], Pleximmune [81560]); **OR**
- Breath testing (eg, Heartsbreath); **OR**
- Combined Gene Expression Profiling and dd-cfDNA tests (eg, OmniGraf); **OR**
- dd-cfDNA tests including, but may not be limited to:
    - myTAI-HEART (0055U); **OR**
    - Viracor TRAC (heart, kidney, liver, lung); **OR**
- HLA testing for transplant rejection (81378 and 81379); **OR**
- kSORT; **OR**
- mDNA and mRNA gene expression tests including, but may not be limited to:
    - MMDx Heart (0087U)
    - MMDx Kidney (0088U)

- MMDx Lung
- TruGraf
- Clarava (0319U); **OR**

- nCounter Human Organ Transplant Panel; **OR**

- RBC antigen genotyping assays (eg, PreciseType HEA test [0001U] and ID CORE XT [0084U]); **OR**

- Urine-based tests for allograft rejection (eg, QiSant [also known as QSant])

A review of the current medical literature shows that the **evidence is insufficient** to determine that these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or acceptable clinical literature examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1	
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)	
81479	Unlisted molecular pathology procedure	
81560	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	
81599	Unlisted multianalyte assay with algorithmic analysis	

84999	Unlisted chemistry procedure	
0018M	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	
0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported	
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma	
0084U	Red blood cell antigen typing, DNA, genotyping of 10 blood groups with phenotype prediction of 37 red blood cell antigens	
0087U	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	
0088U	Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection	
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Appendix

Appendix A

International Society for Heart and Lung Transplantation (ISHLT) System for Grading Rejection[17]

Grade 0R	No rejection	No interstitial cellular infiltrates
Grade 1R	Mild rejection	Interstitial and/or perivascular cellular infiltrate with less than or equal to one focus of myocyte damage
Grade 2R	Moderate rejection	Greater than or equal to two foci of cellular infiltrate with associated myocyte damage
Grade 3R	Severe rejection	Diffuse cellular infiltrate with multifocal myocyte damage, with or without edema, hemorrhage or vasculitis

Change Summary

01/01/2025 New Policy.
05/06/2025 Update, Coverage Change. Coding changes