Molecular Diagnostic Assays and Breath Testing for Transplant Rejection

Humana

Medical Coverage Policy

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Change Summary: Updated Description, References, Appendix

Disclaimer

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:

Gene Expression Profiling

- A **gene expression test** (eg, **AlloMap)** has been developed to predict the likelihood of cardiac rejection. Following a transplant, the test evaluates the quantitative measure of 20 genes using an algorithm to report a rejection risk score. The test is intended to be used in conjunction with standard clinical assessment 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.[33]

- **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 kidney, heart, liver and lung rejection. **(Refer to Coverage Limitations section)**

- **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: **(Refer to Coverage Limitations section)**

  - **Clarava pretransplant mRNA expression assay**

  - **Molecular Microscope Diagnostic system** (eg, **MMDx Heart, MMDx Kidney, MMDx Lung)**

  - **TruGraf Blood Gene Expression Test**

  - **Tutivia post-transplant mRNA expression assay**

- **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.[27] **(Refer to Coverage Limitations section)**

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). (Refer to Coverage Limitations section)**

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.[34] 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. **(Refer to Coverage Limitations section)**

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, **AlloMap and AlloSure Heart [HeartCare], TruGraf and Viracor TRAC Kidney [OmniGraf]). (Refer to Coverage Limitations section)**

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 **(Refer to Coverage Limitations section):**

  - **AlloSure Heart**
  - **AlloSure Kidney**
  - **AlloSure Lung**

- **Prospera Heart**
- **Prospera Kidney with Quantification**
- **Viracor TRAC (heart, kidney, liver and lung)**

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. **(Refer to Coverage Limitations section)**

Coverage Determination

Humana members may be eligible under the Plan for **gene expression profiling** (eg, AlloMap [81595]) for heart transplant recipients who are between one and five years post-transplant.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **gene expression profiling for transplant rejection** for any indications or tests other than those listed above including, but may not be limited to:

- **kSORT; OR**
- **mDNA and mRNA gene expression tests**
  - **MMDx** Heart {0087U)
  - MMDx Kidney {0088U)
  - MMDx Lung
  - TruGraf (0088U)
  - Clarava {0319U)
  - Tutivia {0320U); **OR**
- **nCounter Human Organ Transplant Panel**

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for the **following tests to aid in the diagnosis of transplant rejection:**

- **Antigen-specific T-cell function assays** (eg, CD154+T-cytotoxic memory cells [Pleximark Tx - 0018M, Pleximmune - 81560]); **OR**
- **Breath testing** (eg, Heartsbreath) (0085T); **OR**
- **Combined Gene Expression Profiling and dd-cfDNA tests** (eg, HeartCare, OmniGraf); **OR**
- **dd-cfDNA test** including, but may not be limited to:
  - AlloSure Heart
  - AlloSure Kidney
  - AlloSure Lung
  - Prospera Heart
  - Prospera Kidney with Quantification
  - Viracor TRAC (heart, kidney, liver, lung) **OR**
- **Urine-based tests for allograft rejection** (eg, QiSant [also known as QSant])

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Background

Additional information about **organ transplantation and rejection** may be found from the following websites:

- American College of Cardiology

- American Heart Association
- International Society of Heart and Lung Transplantation
- National Kidney Foundation
- National Library of Medicine

Medical Alternatives

Alternatives to **molecular diagnostic assays and breath testing** include, but may not be limited to, the following:

- Biopsy of the transplanted organ

Physician consultation is advised to make an informed decision based on an individual's health needs.

Provider Claims Codes

Any CPT, HCPCS or ICD codes listed on this medical coverage 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
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
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	**Not Covered**
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subtraction of peripheral blood, algorithm reported as a rejection risk score	

81599	Unlisted multianalyte assay with algorithmic analysis	**Not Covered if used to report any test outlined in Coverage Limitations section**
84999	Unlisted chemistry procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
86849	Unlisted immunology 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	**Not Covered**
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences {94 single nucleotide polymorphism targets and two control targets), plasma	**Not Covered**
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	**Not Covered**
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	**Not Covered**
0118U	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	**Not Covered**
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection	**Not Covered** **New Code Effective 04/01/2022**
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection	**Not Covered** **New Code Effective 04/01/2022**

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 A

International Society for Heart and Lung Transplantation (ISHLT) System for Grading Rejection[23]:

Grade OR	No rejection	No interstitial cellular infiltrates

Grade IR	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