Molecular Diagnostic Assays and Breath Testing for Transplant Rejection

Humana

Medicaid Medical Coverage Policy

Original Effective Date: 01/01/2025
Effective Date: 10/07/2025
Review Date: 10/01/2024
Policy Number: HUM-2158-000
Line of Business: Medicaid
State: KY

Table of Contents

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.[41]

- 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.[35] **(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.[42] 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)
  - VitaGraft Kidney

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** when the following criteria are met:

- Individual is 15 years of age or older; **AND**
- Individual is greater than or equal to 55 days post-transplant; **AND**
- Absence of contraindications/limitations for AlloMap testing; **OR**
- Repeat testing:

  - Year 1 post-transplant – monthly (eg, greater than or equal to 55 days post-transplant through month 12)

  - Years 2 to 3 post-transplant – quarterly (eg, months 15, 18, 21, 24, 27, 30, 33 and 36 post-transplant)

  - Years (greater than or equal to) 4 post-transplant – biannually (eg, months 42, 48, 54, 60, etc.)

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:

- Contraindications/limitations for AlloMap (81595) testing for heart transplant rejection include the following:

    - Individual has had steroid rejection therapy within 21 days prior to testing; **OR**
    - Individual has multiple transplanted organs originating from the same donor; **OR**
    - Individual has received a bone marrow transplant; **OR**
    - Individual is pregnant; **OR**

- 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) (eg, Pleximark Tx [0018M], Pleximmune [81560]); **OR**

- Breath testing (eg, Heartsbreath); **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 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.

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
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	
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	
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	
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma	
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	
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	
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection	
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

References

1. American College of Cardiology (ACC). 2017 ACC/AHA/HFSA/ISHLT/ACP advanced training statement on advanced heart failure and transplant cardiology (revision of the ACC/AHA/ACP/HFSA/ISHLT 2010 clinical competence statement on management of patients with advanced heart failure and cardiac transplant). https://www.acc.org. Published June 20, 2017.

2. American College of Cardiology (ACC). The end of endomyocardial biopsy? A practical guide for noninvasive heart transplant rejection surveillance. https://www.acc.org. Published March 2023.

3. American Society of Transplant Surgeons (ASTS). ASTS Statement on donor derived cell-free DNA (dd-cfDNA). https://www.asts.org. Published March 6, 2023.

4. CareDx, Inc. AlloSure Lung Interpretive Guide. https://caredx.com. Published April 2021.

5. CareDx, Inc. AlloSure Test Results Interpretation Guide. https://caredx.com. Published November 2019.

6. CareDx, Inc. HeartCare Interpretive Guide. https://caredx.com. Updated March 2024.

7. ClinicalKey. Kransdorf EP, Kobashigawa JA. Heart transplantation. In: Felker GM, Mann DL. *Heart Failure: A Companion to Braunwald's Heart Disease*. 4th ed. Elsevier; 2022:1132-1143. https://www.clinicalkey.com.

8. ClinicalKey. Starling, RC. Cardiac transplantation. In: Libby P, Bonow RO, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 12th ed. Elsevier; 2022:1132-1143. https://www.clinicalkey.com.

9. ECRI Institute. Genetic Test Assessment. AlloMap molecular expression test (CareDx, Inc.) for monitoring heart transplant rejection. https://www.ecri.org. Published May 19, 2021.

10. ECRI Institute. Genetic Test Assessment. AlloSure (CareDx, Inc.) for detecting kidney transplant rejection. https://www.ecri.org. Published January 4, 2024.

11. ECRI Institute. Genetic Test Assessment. AlloSure Heart (CareDx, Inc.) for Monitoring Heart Transplant Rejection. https://www.ecri.org. Published November 8, 2023.

12. ECRI Institute. Genetic Test Assessment. AlloSure Lung (CareDx, Inc.) for detecting lung transplant rejection. https://www.ecri.org. Published November 17, 2023.

13. ECRI Institute. Genetic Test Assessment. Molecular diagnostic testing for detecting kidney transplant rejection. https://www.ecri.org. Published January 19, 2024.

14. ECRI Institute. Genetic Test Assessment. Molecular diagnostic testing for monitoring heart transplant rejection. https://www.ecri.org. Published January 10, 2022.

15. ECRI Institute. Genetic Test Assessment. Prospera (Natera, Inc.) for detecting kidney transplant rejection. https://www.ecri.org. Published January 19, 2024.

16. ECRI Institute. Genetic Test Assessment. Prospera Lung (Natera, Inc.) for monitoring lung transplant rejection. https://www.ecri.org. Published April 28, 2022.

17. ECRI Institute. Genetic Test Assessment. QSant (NephroSant) for monitoring kidney transplant rejection. https://www.ecri.org. Published November 1, 2022.

18. ECRI Institute. Genetic Test Assessment. TruGraf Kidney (Transplant Genomics) for detecting risk for kidney transplant rejection. https://www.ecri.org. Published November 4, 2022.

19. ECRI Institute. Genetic Test Assessment. Viracor TRAC kidney dd-cfDNA test (Eurofins Viracor, Inc.) for monitoring kidney transplant rejection. https://www.ecri.org. Published February 23, 2022.

20. ECRI Institute. Genetic Test Assessment. Viracor TRAC lung dd-cfDNA test (Eurofins Viracor, Inc.) for monitoring lung transplant rejection. https://www.ecri.org. Published May 25, 2022.

21. Hayes, Inc. Molecular Test Assessment. AlloSure Kidney (CareDx) for detecting kidney transplant rejection. https://evidence.hayesinc.com. Published May 27, 2021. Updated June 22, 2023.

22. Hayes, Inc. Molecular Test Assessment. Prospera (Natera Inc.). https://evidence.hayesinc.com. Published April 13, 2021. Updated June 15, 2023.

23. Hayes, Inc. Molecular Test Assessment. TruGraf Kidney (Eurofins Transplant Genomics). https://evidence.hayesinc.com. Published January 27, 2022. Updated March 13, 2024.

24. Hayes, Inc. Precision Medicine Research Brief. AlloMap (CareDx). https://evidence.hayesinc.com. Published September 25, 2023.

25. Hayes, Inc. Precision Medicine Research Brief. AlloSure heart (CareDx Inc.). https://evidence.hayesinc.com. Published September 19, 2023.

26. Hayes, Inc. Precision Medicine Research Brief. AlloSure lung (CareDx Inc.). https://evidence.hayesinc.com. Published August 4, 2023.

27. Hayes, Inc. Precision Medicine Research Brief. HeartCare (CareDx). https://evidence.hayesinc.com. Published October 5, 2023.

28. Hayes, Inc. Precision Medicine Research Brief. kSORT Assay (Immucor). https://evidence.hayesinc.com. Published December 5, 2022.

29. Hayes, Inc. Precision Medicine Research Brief. Pleximmune (Plexision). https://evidence.hayesinc.com. Published November 4, 2022.

30. Hayes, Inc. Precision Medicine Research Brief. Prospera heart (Natera Inc.). https://evidence.hayesinc.com. Published September 22, 2023.

31. Hayes, Inc. Precision Medicine Research Brief. TruGraf Liver (Eurofin Transplant Genomics). https://evidence.hayesinc.com. Published January 27, 2022.

32. International Society for Heart and Lung Transplantation (ISHLT). The International Society for Heart and Lung Transplantation guidelines for the care of heart transplant recipients. https://www.ishlt.org. Published August 2010.

33. Sindhi R, Ashokkumar C, Higgs B, et al. Profile of the Pleximmune blood test for transplant rejection risk prediction. *Expert Rev Mol Diagn*. 2016;16:387-393.

34. UpToDate, Inc. Heart transplantation in adults: diagnosis of acute allograft rejection. https://www.uptodate.com. Updated August 2024.

35. UpToDate, Inc. Investigational methods in the diagnosis of acute kidney allograft rejection. https://www.uptodate.com. Updated August 2024.

36. UpToDate, Inc. Kidney transplantation in adults: clinical features and diagnosis of acute renal allograft rejection. https://www.uptodate.com. Updated August 2024.

37. UpToDate, Inc. Kidney transplantation in adults: treatments of acute T cell-mediated (cellular) rejection. https://www.uptodate.com. Updated August 2024.

38. UpToDate, Inc. Liver transplantation in adults: clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft. https://www.uptodate.com. Updated August 2024.

39. UpToDate, Inc. Overview of care of the adult kidney transplant recipient. https://www.uptodate.com. Updated August 2024.

40. UpToDate, Inc. Tools for genetics and genomics: gene expression profiling. https://www.uptodate.com. Updated August 2024

41. US Food & Drug Administration (FDA). 510(k) summary: alloMap molecular expression testing. https://www.fda.gov. Published September 2023.

42. US Food & Drug Administration (FDA). Summary of safety and probable benefit: Heartsbreath. https://www.fda.gov. Published October 23, 2002.

43. US Food & Drug Administration (FDA). Summary of safety and probable benefit: Pleximmune. https://www.fda.gov. Published August 26, 2014.

Appendix

Appendix A

International Society for Heart and Lung Transplantation (ISHLT) System for Grading Rejection[32]

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.