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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Laboratory Tests for Detection of Organ Transplantation Rejection

- AlloSure
- AlloMap® Heart (Molecular Expression Testing, CareDx)
- Heartsbreath Test

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	06/09/2023 Noridian retired MolDX: Allosure® or equivalent Cell-Free DNA Testing for Kidney and Heart Allografts (L38380). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Medicare has incorporated this information within the MolDX: Molecular Testing for Solid Organ Allograft Rejection (L38671) MolDX: Molecular Testing for Solid Organ Allograft Rejection (L38671) MolDX: Molecular Diagnostic Tests (MDT) (L36256)
Local Coverage Article (LCA)	Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection (A58170)

For Non-Medicare Members

Service	Criteria
AlloMap Test	AlloMap is covered for patients who have undergone heart transplant. **If requesting this service, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist • Last 6 months of radiology notes if applicable

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Allosure Test	Donor-derived cell-free DNA testing (e.g., AlloSure) is considered medically necessary when **ALL of the following** criteria are met:
	
	• Patient is 18 years of age or older
	• Patient is at least 14 days post renal transplant
	• A renal biopsy is not already planned or is contraindicated or considered high risk per nephrologist
	• No active BK inflammation based on BK PCR results (will result in false positive)
	
	AND ONE or more of the following representing a clinical suspicion of rejection:
	
	• Creatinine is worsening (≥ 20% above baseline) without an identified cause (e.g., related to medication or dehydration) OR
	• Immunosuppression must be lowered below basal dose for at least one month and if there is a concern for subclinical rejection, one test may be considered medically necessary OR
	• Chronically decreased immunosuppression for persistent leukopenia (post-transplant lymphoproliferative disorder); one test may be medically necessary OR
	• Routine* check for patients with one or more of the following:
	  ○ High pre-transplant Panel Reactive Antibodies (PRA) (> 80%),
	  ○ Pre-existing donor-specific antibodies (DSA)
	  ○ High antigen mismatch (at least 5)
	*Monitoring for subclinical rejection is reasonable in this high risk population, but should not be done more frequently than every 3 months, limited to 3 tests in one year
	
	Not indicated:
	Routine use in otherwise uncomplicated transplant course is ***not*** indicated.

Heartsbreath Test	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies. **If requesting review for this service, please send the following documentation:** • Last 6 months of clinical notes from requesting provider &/or specialist

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

From Southern California Evidence-Based Medicine (EBM) Inquiry Service (July 22, 2020)

Kidney transplantation is the best treatment option for patients with end-stage renal disease. Current surveillance options for allograft injury such as serum creatinine (SCr) and estimated glomerular filtration rate (eGFR), urinalysis, urinary protein, donor specific antibody (DSA), and BK virus surveillance have limitations.

Although biopsy is the gold standard to identify allograft dysfunction, it is an invasive procedure, not without complications, and can encounter challenges including sampling errors, inadequate tissue sample, and variability of interpretation among pathologists. Thus, an urgent need exists for noninvasive and sensitive diagnostic tools for the detection of early rejection that precede a rise in SCr and offer the opportunity to better inform therapeutic decision-making. An emerging area of research are assays that detect donor-derived cell-free DNA (dd-cfDNA), which measure the proportion of total cell-free DNA that is derived from the donor and the recipient. dd-cfDNA assays including AlloSure and Prospera, use targeted amplification and sequencing of single-nucleotide polymorphisms (SNP) to quantify donor and recipient DNA contributions, without the need for prior genotyping of the donor and recipient.

The AlloSure test is intended to assess the probability of allograft rejection in kidney transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of renal biopsy in such patients at least two weeks post-transplant in conjunction with standard clinical assessment. AlloSure is indicated for use in renal transplant patients who are 18 years of age or older and at least 2 weeks (14 days) post-transplant. dd-cfDNA is measured in the blood via targeted amplification and sequencing of a set of carefully selected and validated SNPs. The AlloSure bioinformatics software calculates the percent dd-cfDNA in the sample tested and applies the cut-off values. dd-cfDNA is usually <1% of the total cfDNA when there is no active damage to the allograft. However, during allograft rejection, significantly higher amounts of dd-cfDNA are released into the bloodstream.

A comprehensive search was conducted on July 9, 2020 to identify studies that evaluated the clinical validity and/or clinical utility of AlloSure or Prospera for kidney transplant recipients.

Medical Technology Assessment Committee (MTAC)

AlloSure Test for Kidney Transplant Recipients

Date: 04/26/2021

Evidence Conclusion:

AlloSure:

Clinical validity: Low quality and limited evidence (two studies) showed that AlloSure test may diagnose active rejection in kidney transplants recipients. It has moderate sensitivity & specificity as well as moderate to high NPV. However, more studies are needed to validate its performance.

Clinical utility: There is insufficient evidence to evaluate the impacts of AlloSure on patient management, including the decision to undergo kidney biopsy or change in medication for treatment of active rejection.

There is insufficient evidence, currently, for or against AlloSure test.

Prospera:

Clinical Utility: No studies were identified.

Ongoing Clinical Studies: SCPMG reported three ongoing studies with no posted results.

There is insufficient evidence for or against the use of Prospera for surveillance of rejection.

The use of AlloSure and Prospera for Kidney Transplant Recipients does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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AlloMap in the Detection of Cardiac Allograft Rejection

06/04/2007: MTAC REVIEW

Evidence Conclusion: The CARGO study was an observational study conducted to develop and evaluate a gene expression profiling test (AlloMap test) from peripheral blood mononuclear cells sample to discriminate between quiescence (grade 0 rejection) and moderate /severe (grade >3A) rejection in heart transplant patients, according to the International society for Heart Lung Transplantation (ISHLT) grading. The endomyocardial biopsy (EMB) was used as the gold standard for detecting acute cellular rejection. EMB however has its limitation. It may only detect rejection after cellular infiltration and/or graft damage has occurred and cannot be repeated beyond a certain frequency. In addition, its histopathological interpretation and grading is often not clear-cut, and subject to sampling error and inter observer variability. Overall the results of the study showed that at a predefined threshold of 20 (score range 0-40), the test had an 84% sensitivity to detect a grade >3A rejection compared to the endomyocardial biopsy. After one-year post-transplant the test had a very high negative predictive value (99.6%) i.e. very high ability to rule out moderate /severe rejection. It however had a very low positive predictive value (6.8%) and low specificity (approximately 40%). The study evaluated the ability of the test to discriminate between quiescence and moderate/severe rejection of the transplant. There is no published evidence to date on the clinical outcomes associated with using the test for long-term monitoring of cardiac rejection, on the predictive capacity of the test for future clinical events, or its effect on improving the management of the patients, e.g. tailoring and individualizing immunosuppressive medications. The “Invasive Monitoring Attenuation through Gene Expression” (IMAGE) ongoing study might provide evidence on the long-term health outcomes associated with this gene expression testing.

Articles: The literature search yielded just over 20 articles, the majority of which were reviews and editorials. There was a relatively large observational study (CARGO) that evaluated the ability of gene expressing profiling of peripheral blood test to discriminate between quiescence and from moderate/severe rejection in cardiac allograft recipients, two small case series, and a few other observational studies published in abstract forms. The CARGO study was selected for critical appraisal. Deng MC, Eisen HJ, Mehra MR, et al for the Cardiac allograft Rejection Gene Expression Observational (CARGO) study Investigators. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transplant.2006;6:150-160. See Evidence Table.

The use of AlloMap in the detection of cardiac allograft rejection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

08/19/2003: MTAC REVIEW

Heartsbreath Test in the Detection of Cardiac Allograft Rejection

Evidence Conclusion: The HARDBALL (heart allograft rejection: detection with breath alkanes in low levels) study was a three-year multicenter case-control study supported by the National Heart Lung and Blood Institute (Philips, Boehmer et al. 2004). The original clinical study evaluated a new marker of heart transplant rejection, the breath methylated alkane contour (BMAC) with the idea that rejection is accompanied by oxidative stress which degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes which are excreted in the brain as volatile organic compounds (VOCs). Prior to scheduled EMB, the HBT was employed on 539 heart transplant recipients to collect 1061 breath VOC samples. The breath VOCs were analyzed by gas chromatography and mass spectroscopy, and the BMAC was derived from the abundance of C4-C20 alkanes and monomethylalkanes. The gold standard of rejection was the concordant set of International Society for Heart and Lung Transplantation (ISHLT) grades in biopsies read by two cardiac pathologists. The authors of the HARDBALL study reported that the abundance of breath markers of oxidative stress was significantly greater in grade 0,1 or 2 rejection than in healthy normal persons. Whereas in grade 3 rejection, the abundance of breath markers of oxidative stress was reduced most likely due to accelerated catabolism of alkanes and methyl alkanes that comprise the BMAC. The authors also reported finding that in identifying grade 3 rejection, the negative predictive value of the breath test (97.2%) was similar to EMB (96.7%), and that the breath test could potentially reduce the total number of biopsies performed to assess for rejection in patients at low risk for grade 3 rejection. The sensitivity of the breath test was 78.6% vs. 42.4% with biopsy. However, the breath test had lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than biopsy (specificity 97%, positive predictive value 45.2%). Additionally, the breath test was not evaluated in grade 4 rejection. Breath test results revealed nine breath samples whose levels represented markers of grade 3 rejection. The cross-validated model, indicated that the HBT had a sensitivity of 59.5% and specificity of 58.8% for detecting grade 3 heart transplant rejection, compared to biopsy. The negative predictive value of the breath test for grade 3 rejection was 97.3% such that in a patient with a negative breath test, EMB would contribute little additional clinical information.

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Limitations include a surprising lack of consistency between biopsy interpretation by the pathologists at the transplant program site and the independent pathologist working with the authors. The study results are made difficult to interpret given these disparities. Further studies should investigate the HBT in populations with concurrent patient illness which theoretically, could affect the markers of oxidative stress. It is also important to note that the primary investigator has substantial financial and professional ties with the developer of the device under investigation. The major potential benefit of the HBT would be that it may reduce the risk of a patient getting the wrong treatment because of an erroneous biopsy report. Despite the clear potential benefits that a non-invasive approach such as the HBT could offer, there is no evidence to demonstrate that the use of the HBT will result in better patient management and improvements in health outcomes. Ultimately, a clinically meaningful investigation of the HBT would require assessment in multicenter, outcome-based trials with adequate power, blinding and randomization to control for baseline differences between groups and determine whether additional testing provides a significant advantage over the standard of care in any of the proposed uses of these laboratory tests.

Articles: A search of the PubMed database as well as the Clinical Trials database was completed for the period from database inception through June 2013 for studies on the diagnostic value of the Heartsbreath Test for patients with heart allograft rejection. The search strategy used the terms non-invasive, heart transplant, rejection, Heartsbreath and test with variations. Articles were limited to those published in English language and with enrolled human subjects. The search was supplemented by an examination of article bibliographies in addition to the PubMed related articles function. The HARDBALL study was selected for critical appraisal:

Phillips M, Boehmer JP, Cataneo RN, et al. Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study). *The Journal of Heart and Lung Transplant* 2004;23(6):701-708. See Evidence Table

The use of Heartsbreath test in the detection of cardiac allograft rejection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Allosure- Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
81479	Unlisted molecular pathology procedure
Dx Codes	**Description**
T86.10	Unspecified complication of kidney transplant
Z94.0	Kidney transplant status

AlloMap - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
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

Heartsbreath - Considered Not Medically Necessary:

CPT® Codes	Description
No specific codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.

Date Created	Date Reviewed	Date Last Revised
08/03/2021	08/02/2022[MPC], 08/01/2023[MPC]	08/03/2021

[MPC] Medical Policy Committee

Revision History	Description
12/03/2019	MPC approved a non-coverage policy for Donor-derived cell-free DNA testing (e.g., Allosure)
08/03/2021	Non-coverage for donor-derived cell-free DNA (AlloSure) testing was previously listed on Genetic Screening and Testing criteria. Separate criteria created for donor-derived cell-free DNA after clinical indications for coverage adopted at MPC. Requires 60-day notice, effective date January 1, 2022.
06/23/2023	Merged Allomap and Allosure criteria onto this revised criteria set: Laboratory Tests for Detection of Organ Transplantation Rejection

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