Prior Authorization Review Panel
MCO Policy Submission

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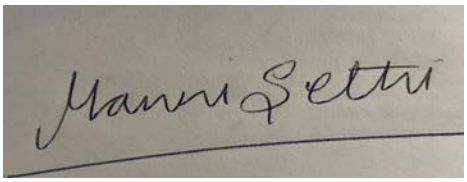
Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 10/1/2023
Policy Number: ccp.1190	**Effective Date:** 10/2015 **Revision Date:** September 1, 2023
Policy Name: Noninvasive blood tests for rejection surveillance after heart transplant	
Type of Submission – Check all that apply: **New Policy** **X Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Noninvasive blood tests for rejection surveillance after heart transplant

Clinical Policy ID: CCP.1190

Recent review date: 9/2023

Next review date: 1/2025

Policy contains: AlloMap, AlloSure, cell-free DNA, Heartsbreath, gene expression profiling; heart transplant, rejection surveillance.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

See also CCP.1363 Immune cell function assay

Gene expression testing using the AlloMap® test (CareDx Inc., Brisbane, California) for rejection surveillance after heart transplantation is clinically proven and, therefore, may be medically necessary for members who are asymptomatic, low-risk for rejection, at least 15 years old, and at least 55 days up to five years post-transplant (ECRI, 2015; U.S. Food and Drug Administration, 2008; Velleca, 2023).

Limitations

All other indications for the AlloMap test are investigational/not clinically proven and, therefore, not medically necessary, including for symptomatic members or for members undergoing routine endomyocardial biopsy.

All other non-invasive tests for rejection surveillance after heart transplantation are investigational/not clinically proven and, therefore, not medically necessary. These include other cell-free donor-derived deoxyribonucleic acid (DNA) testing, Heartsbreath™ (Menssana Research Inc., Fort Lee, New Jersey), AlloSure Heart® (CareDx Inc., Brisbane, California), and other gene expression tests.

Alternative covered services

- Endomyocardial biopsy.

- Primary care and specialty physician (including surgical) evaluation and management.

Background

Heart transplantation is a life-saving procedure for people with end-stage heart failure. While post-transplant care and antirejection drugs have improved long-term outcomes to a three-year survival of 75%, rejection within the first year remains a significant problem to patient survival and to transplanted heart function (National Heart, Lung, and Blood Institute, 2022).

Accordingly, transplant recipients are monitored routinely for antibody-mediated rejection by endomyocardial biopsy, an invasive and uncomfortable procedure with variable accuracy and associated risk. In a study involving eight pediatric centers, 2,665 endomyocardial biopsies were performed in 744 heart transplant recipients. Adverse events occurred in 88 cases (3.3%), of which 28 (1.1%) were high-severity adverse events. Adverse events included tricuspid valve injury, transient complete heart block, and right bundle branch block (Daly, 2012).

Surveillance schedules are transplant center-specific, but generally, are most intense in the first six months to one year, and then decrease in intensity. Heart transplant recipients receive immunosuppressive drugs for life.

Non-invasive tests have been developed for monitoring graft damage and providing an early indication of rejection in heart transplant recipients, which may decrease the need for endomyocardial biopsy. Emerging tests include gene expression profiling, (donor-derived) circulating cell-free DNA, and breath testing. Commercially available tests in the United States include the following:

- AlloMap is a non-invasive, blood-based gene expression test of ribonucleic acid (RNA) isolated from peripheral blood mononuclear cells. It reports a single score between 0 and 40 based on an algorithm composed of the weighted RNA expression levels of 20 analyzed genes. The test result identifies heart transplant recipients with stable allograft function who have a low probability of moderate to severe acute cellular rejection in conjunction with standard clinical assessment (CareDx, Inc., undated). The U.S. Food and Drug Administration (2008) approved its use in heart transplant recipients age 15 years or older and at least two months (≥ 55 days) post-transplant.
- AlloSure Heart is a donor derived cell-free DNA test for detection of acute cell-mediated and antibody-mediated rejection (graft injury) in heart transplant recipients. It uses single nucleotide polymorphisms to distinguish between donor and recipient and complements the AlloMap test; it may serve as a leading, rather than a lagging, indicator of allograft function (Dengu, 2020).
- The Heartsbreath test is used for diagnosing grade 3 rejections. It detects markers of oxidative stress, which may predict rejection. The U.S. Food and Drug Administration (2004) approved the Heartsbreath test under a Humanitarian Use Device for diagnosing grade 3 rejections using markers of oxidative stress, which may predict rejection. It measures volatile organic compounds in alveolar breath and room air by gas chromatography and mass spectrometry, and is to be used as an adjunct to endomyocardial biopsy.

Findings

The International Society for Heart and Lung Transplantation updated its guideline on heart transplant post-surgical care (Velleca, 2023):

- Endomyocardial biopsy is the standard of care for monitoring rejection in the early post-transplant phase and in symptomatic patients. For adult and adolescent heart transplant recipients, periodic endomyocardial biopsy is recommended during the first 6 to 12 postoperative months for surveillance of

graft rejection. In younger children, especially infants, echocardiography may be used as a screening tool to reduce the frequency of endomyocardial biopsy.

- In adult recipients at low risk for acute cellular rejection, gene expression profiling (i.e., Allomap) of peripheral blood can be used between two months (previously recommended six months) and five years after heart transplant to safely reduce the frequency of endomyocardial biopsy. Gene expression profiling in children is not recommended as a routine tool. (Class IIa, Level of Evidence: B).
- The change in recommending gene expression profiling earlier in the post-transplant phase was based on the results of two trials suggesting equivalent clinical outcomes may be attained in patients managed with either a gene expression profiling score or endomyocardial biopsy for acute cellular rejection surveillance at two to six months post-transplant. A gene expression profiling score < 34 (negative predictive value ≥ 98%) could identify patients at low risk for rejection as early as two to six months after transplantation without an increase in adverse outcomes (Crespo-Leiro, 2016, n = 328; Kobashigawa, 2015, n = 30).

In 2022, the American Society of Transplantation's Thoracic and Critical Care Community of Practice held an expert panel conference to provide guidance on use of biomarkers in heart transplantation. Endomyocardial biopsy plays an important role in management of heart transplant recipients but is imperfect for detecting rejection. The most impactful use of biomarkers/diagnostic tests in heart transplantation is risk stratification. For screening purposes, negative predictive value demonstrates minimal risk, but for a diagnostic test, high positive predictive value will guide clinical practice. Gene expression profiling has clinical utility as a screening test to indicate the absence of cellular rejection, but it cannot detect antibody mediated rejection (Kobashigawa, 2023).

A position statement of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society endorsed use of endomyocardial biopsy in rejection surveillance for heart transplants. The statement noted that biopsy can be used in asymptomatic patients or in those with worsening clinical status, even though consensus is lacking in optimal timing and frequency. Techniques such as gene expression profiling and donor-derived cell-free DNA, should be explored in prospective clinical trials to assess the optimal approach to rejection surveillance (Seferovic, 2021).

The strongest evidence supports the clinical validity of the AlloMap test using data from the Outcomes AlloMap Registry. For other non-invasive rejection surveillance tests, systematic reviews and individual studies, often from the same investigator groups, provide low-quality evidence of analytic validity but lack independent confirmation of clinical validity or clinical utility.

The intent of AlloMap gene expression assessment is to provide a non-invasive alternative to endomyocardial biopsy. Because of limitations in the evidence base and in its ability to assess only the risk of acute cellular rejection and not rejection itself, its use in lieu of endomyocardial biopsy should be limited to select patients. The evidence supports AlloMap as a test to “rule-out” the risk of graft rejection in patients more than six months post-transplant who do not exhibit symptoms of rejection. It is not intended for patients exhibiting clinical symptoms of rejection, who would undergo endomyocardial biopsy.

Results of other non-invasive tests are presented below. Their results tend to provide more favorable opinions of individual non-invasive tests but lack rigorous examination of test efficacy compared to patients monitored with guideline- or center-directed endomyocardial biopsy.

AlloMap

A systematic review included three studies that addressed the clinical validity and clinical utility of the AlloMap test. The three included studies provided the validity data submitted for regulatory approval. In participants longer than six months post-transplant and longer than 30 days after administration of immunosuppressive therapy for treating rejection, the negative predictive value of AlloMap was considered high (98.8% to 100%). There were

insufficient data to determine the negative predictive value for AlloMap in patients less than six months post-transplant or the sensitivity for detecting acute cellular rejection at any point post-transplant. There were insufficient data from two of the studies to determine the test's clinical utility in terms of mortality, number of biopsies, biopsy-related adverse events, or quality of life compared with the endomyocardial biopsy cohorts, although preliminary evidence suggests comparable outcomes (ECRI, 2015).

One analysis included 1,504 adult heart transplant patients who underwent surveillance with the AlloMap test. Among those selected for surveillance, survival was 99%, 98%, and 94% after one, two, and five years, respectively. Moderate to severe acute cellular rejection rates were 2.0% from two to six months and 2.2% after six months, considered low by the authors (Moayedi, 2019b).

A study of 933 heart transplant patients in the Outcomes AlloMap Registry showed that African Americans had a significantly higher adjusted mortality rate than did Caucasians (P = .007). The gene expression profiling score was associated with increased mortality among Caucasians (P = .048), but not African Americans (Moayedi, 2019a).

A study of 737 heart transplant recipients reviewed the ability of AlloMap gene expression profiling to predict if a recipient is at low risk for rejection. A subset of 36 patients with a composite event and 55 controls (with no event) were compared, and the ability of profiling to predict low risk within three years after surgery was strong (negative predictive value 97%, positive predictive value 35.4%) (Crespo-Leiro, 2015).

The prior 2015 study was validated by a separate group of experts the following year. In 399 of the 737 patients, the AlloMap gene expression test resulted in a 95.5% true negative rate, and a 10.2% true positive rate (Crespo-Leiro, 2016).

AlloSure/circulating cell-free DNA

DNA originating from the transplanted organ has been proposed as a biomarker for organ rejection and immunosuppression optimization. Levels of donor-derived, cell-free DNA in the blood is usually highest immediately after solid organ transplantation and generally decreases over time to very low levels. Its measurement has required both donor and recipient genotyping, making it difficult to quantify and use clinically. The AlloSure test measures circulating donor-derived cell-free DNA without the need for separate genotyping (Edwards, 2022).

The analytic performance of the AlloSure sequencing assay demonstrates increased levels of donor-derived cell-free DNA in patients with biopsy-confirmed rejection and decreased levels after successful rejection treatment, providing results in three days (Grskovic, 2016). Studies of clinical validity described below suggest its potential as a noninvasive tool for screening and monitoring allograft health because of its high negative predictive value, but it has low specificity for detecting underlying injury from rejection or infection. Further studies are required to validate threshold values and determine its clinical use. A registry study to assess the clinical utility of a combined AlloMap and AlloSure testing service called "HeartCare" as part of their post-transplant management is in progress (ClinicalTrials.gov, 2023).

A study of 2,164 samples from 740 heart transplant assessed the ability of donor-derived cell-free DNA tests to monitor for rejection. At a 0.2% threshold, donor-derived cell-free DNA had a 44% sensitivity to detect rejection and a 97% negative predictive value (Khush, 2019).

A quasi-systematic review of 11 studies of cell-free DNA surveillance, including AlloSure, for heart transplant rejection revealed a link between acute rejection (found by endomyocardial biopsy) and DNA levels in most studies, reflecting a high negative predictive value. However, complex methodology and lack of standardization of collection, analysis, and reporting of the results currently limit its clinical potential (Sharma, 2021).

In 2022, we updated the references and found no additional research on volatile organic compounds in alveolar breath as biomarkers for heart transplant rejection. We modified the coverage statement to include asymptomatic as a criterion for medical necessity.

In 2023, we updated the recommendations from the International Society for Heart and Lung Transplantation (Velleca, 2023) and added recommendations from the American Society of Transplantation (Kobashigawa, 2023). We added results of two validation studies of donor-derived cell-free DNA testing for heart allograft rejection, with no policy changes warranted:

- In 144 adult and pediatric participants, donor fraction cell-free DNA testing at a threshold of 0.14% predicted the risk of rejection after heart transplantation in both pediatric and adult patients with a sensitivity of 67%, a specificity of 79%, a positive predictive value of 34%, a negative predictive value of 94%, and an area under the curve of 0.78 for detecting rejection (Richmond, 2023).
- A retrospective study compared two standard and expanded standard single nucleotide polymorphism donor-derived cell-free DNA tests and gene expression profiling performed within 14 days of endomyocardial biopsy (n = 112). There were no significant differences in the ability of standard and expanded donor-derived cell-free DNA to detect acute cellular rejection ($P < .001$) with low sensitivity (39%) but high specificity (82% and 84%). Gene expression profiling did not improve sensitivity and showed worse specificity ($P < .001$) compared to standard donor-derived cell-free DNA. Prospective controlled studies are needed (Rodgers, 2023).

References

On June 13, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “AlloMap,” “AlloSure,” “cell-free DNA,” “Heartsbreath,” “heart transplant,” and “rejection surveillance.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

9/2015: initial review date and clinical policy effective date: 10/2015

9/2016: Policy references updated.

9/2017: Policy references updated.

9/2018: Policy references updated.

9/2019: Policy references updated. Policy ID changed to CCP.1190.

9/2020: Policy references updated. Major changes made.

9/2021: Policy references updated.

9/2022: Policy references updated. Coverage modified.

9/2023: Policy references updated.