Medical Policy

Current Effective Date: 12/29/24
Status: Approved
Reviewed by Medical Policy Subcommittee: 11/2/17, 5/9/19, 2/3/22, 12/14/23, 12/29/24
Reviewed Dates: 11/2/17, 5/9/19, 2/3/22, 12/14/23, 12/2/24

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**Title**

**Heart Transplantation Rejection Monitoring Policy**

**Indication/Usage:**

Despite immunosuppressive therapy, cardiac allograft rejection remains a constant complication post cardiac transplantation with the most frequent allograft rejection occurring within the first month post-transplant and declines thereafter. Survival depends on timely, accurate monitoring of allograft rejection and graft dysfunction. Endomyocardial biopsies examine microscopic changes in heart tissue must be completed regularly to detect for signs of rejection. However, myocardial

biopsies are invasive and have limitations such as they can only detect rejection once cellular infiltration and/or graft damage has occurred, are uncomfortable and carry risks of serious complications.

International Society of Heart and Lung Transplantation (ISHLT) Grading System for Acute Cellular Rejection (Baran, 2010

| Grade | Results interpretation |
|---|---|
| 0 | No rejection |
| 1R | Mild-Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage |
| 2R | Moderate-≥foci of infiltrate with associated myocyte damage |
| 3R | Severe-diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage or vasculitis |

FDA approved non-invasive testing methods for heart transplant rejections monitoring:

**Allomap™ Molecular Expression Testing**: AlloMap™ molecular expression testing is a noninvasive assay that targets immune cells in the peripheral blood that cause and respond to cardiac rejection. By measuring patterns of activity of a number of genes, rejection can be diagnosed and predicted. Possible scores range from 0 to 40, with higher scores more strongly correlated with histologic rejection. AlloMap molecular expression testing may allow physicians to reduce biopsies and manage immunosuppressive therapy while achieving a better balance between prevention of rejection and immune suppression complications.

**Heartsbreath™:** Heartsbreath™ i**s** a non-invasive breath test for markers that predict the probability of grade 3 rejection in heart transplant recipients who received their transplant within the preceding year (Menssana, 2004).

**Medical Indications for Authorization**

**Commercial and Medicare Members**

SummaCare covers genetic expression profile (AlloMap™) instead of endomyocardial biopsy as **medically necessary** (every 1-3 months) when results will be used to determine the need for subsequent endomyocardial biopsy to clarify rejection status when **ALL** the following criteria are met:

1. 15 years or older **and**
2. Six months to five years post-heart transplantation **and**
3. No episodes ACR in past 6 months **and**

Heart allograft is stable as demonstrated by **ALL** the following criteria:

- Absence of signs or symptoms of congestive heart failure

- Recent echocardiogram with left ventricular ejection fraction (LVEF) ≥ 45%
- No signs of severe cardiac allograft vasculopathy
- Low probability of moderate or severe acute cellular rejection as demonstrated by **BOTH** of the following criteria: ○ International Society of Heart and Lung Transplantation (ISHLT) rejection status Grade 0R or 1R on all previous endomyocardial biopsies **and**
    - ○ No history or evidence of antibody mediated rejection

4. No history of elevated genetic expression profile that prompted subsequent endomyocardial biopsy to clarify rejection status

**Heartsbreath™:** SummaCare does not cover and finds Heartsbreath™ **not medically necessary**, experimental and investigational. There is insufficient evidence to conclude that the breath test for management of post-cardiac transplantation rejection will result in improved management

There are no Centers for Medicare and Medicaid National or Local Coverage Decisions for

**AlloMap™.**

**Heartsbreath™:** Effective for services performed on or after December 8, 2008, the Centers for Medicare & Medicaid Services has determined that the evidence does not adequately define the technical characteristics of the test nor demonstrate that Heartsbreath™ testing to predict heart transplant rejection improves health outcomes in Medicare beneficiaries. Thus, we conclude that the Heartsbreath test is not reasonable and necessary under section 1862(a) (1) (A) of the Social Security Act and is non-covered (Center for Medicare and Medicaid Services, 2008).

**Limitations**

Limitations for Allomap include:
Heart transplant recipients that are acutely symptomatic
Recurrent rejections
Individuals receiving high dose steroids within last 3 weeks
Blood transfusion or hematopoietic growth factor affecting leukocytes in the last 30 days
Pregnancy
Signs and symptoms of cardiac allograft dysfunction or hemodynamic compromise

**Coverage Decisions**

Coverage decisions made per CMS, Hayes and industry standards research

**Plans Covered By This Policy**

Commercial and Medicare
Self-funded Commercial groups refer to plan document for coverage

**Sources Reviewed**

Baran, D. A. (2010). The international society of heart and lung transplantation guidelines for the care of heart transplant recipients. *The Journal of Heart and Lung Transplantation*, 914-956.

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Crespo-Leiro, M. M. (2016). Clinical Usefulness of gene-expression profile to rule out acute rejection after heart transplantation. *European Heart Journal*, 2591-2601.

Deng, M. M. (2017). The AlloMap genomic biomarker story: 10 years after. *Wiley Clinical Transplantation: The Journal of Clinical and Transplantational Research*.

FDA. (2004, February 24). *Humanitarian Device Exemption (HDE)*. Retrieved August 18, 2017, from Heartsbreath: Test, Volatile Organic Compounds Breath Analysis: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=h030004

FDA. (2008, August 26). *Device Classification under Section513 (f)(2)(denovo)*. Retrieved August 18, 20017, from Cardiac Allograft Gene Expression Profiling Test System: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=den080007

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year. The Heartsbreath™ test is intended to be used as an adjunct to, and not as a substitute for Phillips, M. M. (2004). Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL Study). *The Journal of Heart and Lung Transplantation*, 701-708.

Products, M. (2004). *Menssana Research, INC.* Retrieved 08 18, 2017, from Point-of-care-breath testHeart Transplant Rejection (Heartsbreath)/Menssana Products: http://www.menssanaresearch.com/products_Heartsbreath_heart_transplant_rejection_Menssana.html

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