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Heart Transplantation Rejection Monitoring

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

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**
4. 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
5. 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

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

SummaCare does not cover genetic expression profile (i.e., AlloMap) for any other indication as it is considered experimental, investigational or unproven.

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.

Limitations for AlloMap

- Limitations 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

Research Summary[HD4]

Allomap™: The Cardiac Allograft Rejection Gene Expression Observational study (CARGO) was initiated in 2001 to study the utility of peripheral blood gene expression for cardiac transplantation acute rejection management. The CARGO study and the team at CareDx (formerly XDxInc) developed and validated gene expression profiling test of peripheral blood mono-nuclear cell gene expression based on comprehensive gene array analysis and DNA-library screening, real-time PCR validation, and bioinformatics post-processing. The test, developed against the phenotype reference of endomyocardial biopsy (EMB)-based monitoring, allowed to identify stable heart transplant patients with a low probability of moderate/severe acute cellular cardiac allograft rejection. Based on this test, a clinical algorithm comprising of routine surveillance clinical visits, non-invasive graft function testing by echocardiography, and AlloMap™ testing was implemented since 2005 (Deng, 2017). The CARGO study resulted in the identification and validation of gene expression patterns in peripheral blood that correlate with acute rejection. Using these genes, which encompass multiple biological pathways, a multi-gene test panel was developed that can distinguish quiescence from acute rejection. The algorithm outcome is a single score that considers the contribution of each gene in the panel. This score correlates strongly to immune status and may also be able to predict the occurrence of future rejection and graft dysfunction. Physicians are expected to combine the algorithm score with other criteria to make clinical decisions. Since the original CARGO study was completed, results of at least two other studies also have been published. These studies are CARGO II, the European version of CARGO, and the Invasive Monitoring Attenuation through Gene Expression (IMAGE) clinical trial, a multicenter clinical trial of stable heart transplant patients conducted at 12 heart transplant centers in the U.S. Both CARGO II and IMAGE indicated that AlloMap™ testing was non-inferior to conventional endomyocardial biopsy (EMB) for monitoring post-transplant patients with stable allograft function who have a low probability of moderate/severe acute allograft rejection (Crespo-Leiro, 2016). IMAGE results showed that during a median follow-up of 19 months, cardiac transplant

recipients monitored with AlloMap™ had similar two-year cumulative rates of rejection with hemodynamic compromise, graft dysfunction from other causes, death or retransplantation as those monitored with routine biopsies (14.5 percent vs. 15.3 percent) (Deng, 2017). Hayes (2010) points out, though, that only 6 of 34 (18%) treated episodes of rejection were detected in the geneexpression group. The other 28 (82%) episodes were detected on clinical assessment or echocardiography. Hayes (2010) postulates that once low-risk patients are 6 months posttransplant neither blood testing nor biopsies are required to predict rejection.

Heartsbreath™: The Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL study)
A new marker of heart transplant rejection is the breath methylated alkane contour (BMAC). Cardiac allograft rejection is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes, which are excreted in the breath as volatile organic compounds (VOCs). Breath VOC samples (n = 1,061) were collected from 539 heart transplant recipients before scheduled endomyocardial biopsy. Breath VOCs were analyzed by gas chromatography and mass spectroscopy, and 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 2 reviewers. Concordant biopsies were: Grade 0, 645 of 1,061 (60.8%); 1A, 197 (18.6%); 1B, 84 (7.9%); 2, 93 (8.8%); and 3A, 42 (4.0%). A combination of 9 VOCs in the BMAC identified Grade 3 rejection (sensitivity 78.6%, specificity 62.4%, cross-validated sensitivity 59.5%, crossvalidated specificity 58.8%, positive predictive value 5.6%, and negative predictive value 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, positive predictive value 45.2% and negative predictive value 96.7%. A breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 heart transplant rejection than a biopsy reading by a site pathologist, but the negative predictive values of the 2 tests were similar. A screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and reduce the number of endomyocardial biopsies. The results were published in 2004 (Phillips).

Coverage Decisions

FDA U.S. Food & Drug Administration:
AlloMap™: AlloMap was developed by XDx, a molecular diagnostics company based in Brisbane, CA. The XDx laboratory that performs AlloMap testing is CLIA-certified. AlloMap has been available since 2005 and was cleared by the U.S. Food and Drug Administration in 2008 (FDA, 2008).
Heartsbreath™: Approval Order Statement
Approval for the Heartsbreath™. This device is indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath™ test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy within the previous month (FDA, Humanitarian Device Exemption (HDE), 2004).

Centers for Medicare and Medicaid Coverage Decisions:
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).
Heartsbreath™:
No plans could be found that provide coverage for Heartsbreath™

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.

Center for Medicare and Medicaid Services. (2008, December 8). Retrieved August 18, 2017, from Decision Memo for Heartsbreath Test for Heart Translant Rejection (CAG-00394N).

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

https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=4860

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 test-Heart Transplant Rejection (Heartsbreath)/Menssana Products: http://www.menssanaresearch.com/products_Heartsbreath_heart_transplant_rejection_Menssana.html

https://www.cms.gov/medicare
https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=325&ncdver=1