Clinical Policy Title: Noninvasive tests for rejection surveillance after heart transplantation

Clinical Policy Number: 1190

Effective Date: January 1, 2016
Initial Review Date: September 16, 2015
Most Recent Review Date: August 1, 2018
Next Review Date: August 2019

Policy contains:

- AlloMap Dx.
- Heartsbreath.
- Mycophenolic acid.
- Echocardiograph.

Related policies:

None

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s 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 Prestige Health Choice 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. Prestige Health Choice’s 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. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of non-invasive tests for rejection surveillance after heart transplantation to be clinically proven and, therefore, medically necessary when the following criteria are met (Chruscinski 2016, Daly 2015, Lipschultz 2014, Andalusian Agency for Health Technology Assessment 2012, Blue Cross Blue Shield Technology Evaluation Center 2011):

- Endomyocardial biopsy is not technically feasible (e.g., anatomic conditions precluding catheterization and biopsy).
- The patient’s physical condition creates excessive or life-threatening risk for endomyocardial biopsy to be attempted.

Limitations:
Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of non-invasive tests for rejection surveillance after heart transplantation are considered investigational and, therefore, not medically necessary.

**Alternative covered services:**

- 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. The first transplant was performed in 1967. While post-transplant care and antirejection drugs have improved long-term outcomes to a median survival of 10 years, rejection within the first year remains a significant problem to patient survival and to transplanted heart function. Accordingly, transplant recipients are routinely monitored for rejection by endomyocardial biopsy, an invasive and uncomfortable procedure that is not without risk. A number of noninvasive tests, including the AlloMap genetic test, the Heartsbreath test, mycophenolic acid, and echocardiographic indices are under investigation. Surveillance schedules are transplant center-specific, but generally, most intense in the first six months to one year and then decreasing in intensity. Patients with transplanted hearts receive immunosuppressive drugs for life.

Genetic testing or gene expression testing includes a variety of laboratory tests (analysis of deoxyribonucleic acid [DNA], ribonucleic acid [RNA], genes, or gene products) for the purposes of:

- Diagnosing disease.
- Assisting in treatment decisions.
- Early identification of and intervention to control rejection.
- Predicting future disease, identifying carriers of disease, or prenatal testing.

Heartsbreath test is used for diagnosing grade 3 rejections. It detects markers of oxidative stress, which may predict rejection. Mycophenolic acid is an immunosuppressant drug used to prevent rejection of solid organ transplants (including hearts). Monitoring mycophenolic acid has the objective of improving control over acute rejection and is based on observed associations (i.e., hypothesis-generating rather than -testing studies) between mycophenolic acid pharmacokinetics and rejection in adults and children.

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
• Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
• The Centers for Medicare & Medicaid Services.

We conducted searches on June 8, 2018. Search terms were: "heart transplant (MeSH)," "rejection (MeSH)," and "allograft (MeSH)."

We included:
• Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• Guidelines based on systematic reviews.
• Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Lipschultz (2014) reviewed clinical success in identifying limitations in solid-organ transplant-related issues. In terms of antibody-mediated rejection, an area requiring further attention is the allograft injury caused by the binding of C1q to donor specific antibodies. The authors postulated that therapies that target C1q can help prevent chronic allograft injury.

Chruscinski (2016) piloted a microarray technique and compared pre-transplant sera from 24 heart failure patients who subsequently received heart transplants. The authors identified eight antibody reactivities that were higher in patients who developed cellular rejection (two or more episodes of significant rejection in first year after transplant as defined by revised criteria from the International Society for Heart and Lung Transplantation) compared with those who did have not have rejection episodes. In a second retrospective study with 31 patients, seven IgM reactivities were identified that were higher in heart transplant recipients who developed antibody-mediated rejection compared with control recipients, and in time course studies, these reactivities appeared prior to overt graft dysfunction. The technique demonstrated improved sensitivity compared to traditional methods and suggests that this autoantibody array technology may help identify patients at risk of rejection following heart transplantation and identify heart transplant recipients with antibody-mediated rejection.

Policy updates:

A narrative review (Daly 2015) noted that heart transplantation is associated with high rates of overall survival in children with end-stage heart failure. A pediatric heart donation priority list in Britain relies on ABO blood group screening so that the most severely afflicted infants and children may be prioritized to earlier therapeutic intervention. The review also identifies factors that complicate and contribute to failure
in pediatric heart transplantation, including allosensitization. The authors emphasize the usefulness of biomarkers to detect acute cellular rejection and cardiac allograft vasculopathy (e.g., VEGF-A).

We did not identify any new peer-reviewed publications or guidelines in 2018. The National Coverage Determination for Heartsbreath test for heart transplant rejection (260.1) was added to the policy. The Centers for Medicare & Medicaid Services has concluded that because the evidence does not sufficiently define the technical characteristics of the Heartsbreath test nor demonstrate that it improves outcomes in Medicare beneficiaries, it is not reasonable and necessary and therefore it is not covered. Policy ID changed from 04.01.04 to CCP.1190.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Chruscinski (2016) | **Key points:**  
  - Narrative review of a new test for autoantibodies after heart transplantation.  
  - The authors proposed a custom antigen microarray technique that can simultaneously measure IgM and IgG reactivities against 64 unique antigens using just five microliters of patient serum.  
  - There is evidence that these autoantibodies contribute to cardiac dysfunction and correlate with clinical outcomes.  
  - The technique displayed enhanced sensitivity to detect autoantibodies compared to the traditional ELISA method. |
| Daly (2015) | **Key points:**  
  - Narrative review opines that heart transplantation has been so successful that the number of potential recipients continues to exceed the number of available donors.  
  - Developing strategies to safely increase donor utilization is crucial to decreasing wait-list mortality.  
  - A new pediatric heart allocation policy is set to be implemented with the goal of prioritizing the most urgent listed candidates.  
  - Biomarkers for acute cellular rejection, such as donor-specific cell-free DNA, and cardiac allograft vasculopathy, such as VEGF-A, may lead to a decreased need for invasive screening. |
| Lipschultz (2014) | **Key points:**  
  - Reviewed clinical success in solid-organ transplant-related issues.  
  - Allograft injury caused by the binding of C1q to DSAs requires further attention.  
  - Suggests therapies targeting C1q can help prevent chronic allograft injury. |
| Andalusian Agency for Health Technology Assessment (2012) | **Key points:**  
  - Included: two evidence reports.  
    - Four diagnostic accuracy studies.  
    - One clinical trial.  
    - One simple cost study; adequate/high methodologic quality.  
  - Diagnostic accuracy: sensitivity, 71% – 100%; specificity, 42% – 79%; positive predictive value, 1.3 – 3.6; negative, 0 – 0.58. |
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|          | • Accuracy indicates best used for ruling out disease.  
|          | • Clinical trial: No statistically significant difference in rejection risk during 19-month follow-up. |
| Blue Cross Blue Shield Technology Evaluation Center (2011) Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection | Key points:  
|          | • Validation studies conducted in non-representative small samples with low-grade rejection.  
|          | • English-language test performance studies, September 2011.  
|          | • Accuracy: sensitivity, 76% – 84% (cutoff score 20); specificity, 38% – 41% (20).  
|          | • Post-hoc analyses (six and 12 months after transplant): Se, 71.4 – 80. Sp, 77.8 – 78.7.  
|          | • One randomized controlled trial (Pham 2010) compared outcomes (AlloMap versus biopsy): two-year composite outcome similar in both groups; fewer biopsies in AlloMap group, but detection of asymptomatic rejection higher in biopsy group; composite outcome may not be sensitive to differences in treated rejection episodes.  
|          | • Conclusion: meets Technology Evaluation Center criteria, final regulatory approval; improvement to net health outcome/as beneficial as established alternatives; available outside investigational setting. |
| Hayes (2011) AlloMap molecular expression (XDi Inc.) for detection of heart transplant rejection | Key points:  
|          | • Alternate to endomyocardial biopsy.  
|          | • Under investigation. |
| Pham (2010) Gene expression profiling for rejection surveillance after cardiac transplantation | Key points:  
|          | • Non-inferiority comparison: endomyocardial biopsy versus gene expression profiling: 602 patients ≥ 18 years transplanted ≥ 6 months to 5 years: 1:1 ratio assignment with stratification by treatment center and interval since transplant (≤ 1 year 2-3.4-5).  
|          | • Surveillance by protocols at treatment centers and all patients also received clinical and echocardiographic assessments.  
|          | • Sponsored by test manufacturer.  
|          | • First occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or re-transplantation (primary).  
|          | • Death from any cause, number of biopsies performed, and biopsy-related complications (secondary).  
|          | • Quality of life and satisfaction with method of monitoring (SF-12).  
|          | • Baseline characteristics of groups well-matched except for higher proportion of blacks in biopsy.  
|          | • During median follow-up of 19 months: AlloMap and biopsy groups had similar outcomes. |
| Oremus (Agency for Healthcare Research and Quality 2008) Utility of monitoring mycophenolic acid in solid organ transplant recipients | Key points:  
|          | • Knowledge still in infancy.  
|          | • Until there is more evidence, stakeholders should decide on case-by-case basis whether possible but uncertain benefits are worth extra time and expense. |


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<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Mena (2006)</td>
<td><strong>Key points:</strong>&lt;br&gt;• Studies using biopsy as a reference standard, 1967 –July 2005.&lt;br&gt;• Indices evaluated: mitral inflow velocities (early and late diastolic wave peak velocities, pressure half time, and isovolumetric relaxation time).&lt;br&gt;• Evidence currently available limited to diagnostic accuracy and does not support use.</td>
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</tbody>
</table>

**References**

**Professional society guidelines/other:**

Carbaliddo FM, Llanos Méndez A. *AlloMap genetic test for cardiac transplant rejection*. Seville, Spain: Andalusian Agency for Health Technology Assessment (AETSA); 2012.


*Gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection*. Chicago, IL: BlueCross BlueShield Technology Evaluation Center; 2011.


**Peer-Reviewed References**


**Centers for Medicare & Medicaid Services National Coverage Determination:**

National Coverage Determination for Heartsbreath Test for Heart transplant rejection (260.10)

**Local Coverage Determinations**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes:**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<tr>
<th>CPT Code</th>
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<tr>
<td>0085T</td>
<td>Heartsbreath</td>
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<tr>
<td>80180</td>
<td>Mycophenolate (mycophenolic acid)</td>
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<td>81595</td>
<td>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</td>
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<td>93306</td>
<td>Echocardiography, transthoracic, real-time with image documentation</td>
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<td>T86.21</td>
<td>Heart transplant rejection</td>
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<td>T86.290</td>
<td>Cardiac allograft vasculopathy</td>
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