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

Clinical Policy Number: 04.01.04

Effective Date: January 1, 2016
Initial Review Date: September 16, 2015
Most Recent Review Date: September 21, 2016
Next Review Date: September 2017

Related policies:

None.

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

Coverage policy

Keystone First 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:

- 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:

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 (MPA) is an immunosuppressant drug used to prevent rejection of solid organ transplants (including hearts). Monitoring MPA has the objective of improving control over acute rejection and is based on observed associations (i.e., hypothesis-generating rather than -testing studies) between MPA pharmacokinetics and rejection in adults and children.

Searches

Keystone First 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 (CMS).

We conducted searches on August 30, 2016. 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 (AMR), an area requiring further attention is the allograft injury caused by the binding of C1q to donor specific antibodies (DSAs). The authors postulated that therapies that target C1q can help prevent chronic allograft injury.

**Policy updates:**

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 (AMR) 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 AMR.

**Summary of clinical evidence:**
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Chruscinski (2016) | **Generation of antigen microarrays to screen for autoantibodies in heart failure and heart transplantation.**  
**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. |
| Lipschultz (2014) | **Issues in solid organ transplantation in children: translational research from bench to bedside**  
**Key points:**  
- Reviewed clinical success in solid-organ transplant-related issues.  
- In terms of AMR, an area requiring further attention is the allograft injury caused by the binding of C1q to DSAs)  
- Suggested that therapies targeting C1q can help prevent chronic allograft injury. |
| Andalusian Agency for Health Technology Assessment (2012) | **AlloMap genetic test for cardiac transplant rejection.**  
**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.  
- Accuracy indicates best used for ruling out disease.  
- Clinical trial: NS 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 RCT (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 TEC criteria, final regulatory approval; improvement to net health outcome/as beneficial as established alternatives; available outside investigational setting. |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Hayes (2011)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| AlloMap molecular expression (XDx Inc.) for detection of heart transplant rejection | • Alternate to endomyocardial biopsy.  
• Under investigation. |
| Pham (2010)                 | **Key points:**                   |
| Gene expression profiling for rejection surveillance after cardiac transplantation. | • 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) | **Key points:**                   |
| Utility of monitoring mycophenolic acid in solid organ transplant recipients. | • 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. |
| Mena (2006)                 | **Key points:**                   |
• Indices evaluated: mitral inflow velocities (early and late diastolic wave peak velocities, pressure half time, and isovolumetric relaxation time).  
• Evidence currently available limited to diagnostic accuracy and does not support use. |

**Glossary**

**Allotransplantation (allograft)** — Transplantation of cells, tissues, or organs to a recipient from a genetically non-identical (i.e., not self or identical twin) donor of the same species.
**Compassionate Use** — Also known as “expanded access,” a term as defined by the Food and Drug Administration (FDA) to represent the use of a drug or clinical treatment “outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. FDA regulations allow access to investigational drugs for treatment purposes on a case-by-case basis for an individual patient, or for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial.” (http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.htm). Accessed August 26, 2016.

**Echocardiographic diastolic indices** — Characteristics of a cardiac sonogram used to evaluate left ventricular function. Those which have been suggested as potential indicators of transplant rejection include: mitral inflow velocity, isovolumetric relaxation time, velocity of propagation of left ventricular color Doppler inflow, pulmonary vein Doppler flow, and tissue Doppler.

**Endomyocardial biopsy** — A diagnostic procedure mainly used to confirm sufficiency of immunosuppressive therapy after cardiac transplantation. It is performed via catheter under local anesthesia. Although it is generally safe (mortality rates from 0 percent – 0.4 percent), potential complications such as perforation/pericardial tamponade can be life-threatening.

**Gold/reference standard (for diagnostic tests)** — The criterion standard for diagnosis; hypothetically, the test with 100 percent sensitivity, or that which correctly identifies all individuals with a disease. In many cases, this has been and remains light microscope histopathology.

**Heartsbreath test** — For diagnosing grade 3 rejection. It detects markers of oxidative stress, which may predict rejection.

**Mycophenolic acid (MPA)** — An immunosuppressant drug used to prevent rejection of solid organ transplants (including hearts). Monitoring MPA has the objective of improving control over acute rejection and is based on observed associations (i.e., hypothesis-generating rather than -testing studies) between MPA pharmacokinetics and rejection in adults and children.

**Transplant rejection** — The immune system of the transplant recipient recognizes the organ or tissue as foreign and reacts against it by mobilizing white blood cells (lymphocytes) and other components of an immune response as in response to infections. Symptoms and signs include organ dysfunction, feeling unwell, uneasy, or feverish. Heart transplant rejection is common during the first year and diagnosed by endomyocardial biopsy (on a routine monitoring schedule or in response to symptoms). Rejection is graded by the International Society for Heart and Lung Transplantation (ISHLT) score:

<table>
<thead>
<tr>
<th>ISHLT grade</th>
<th>Biopsy characteristics</th>
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<tbody>
<tr>
<td>0</td>
<td>No rejection</td>
</tr>
<tr>
<td>Level</td>
<td>Description</td>
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<tr>
<td>-------</td>
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<tr>
<td>1 R, mild</td>
<td>Interstitial and/or peri-vascular infiltrate with up to one focus of myocyte damage</td>
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<tr>
<td>2 R, moderate</td>
<td>Two or more foci of infiltrate with associated myocyte damage</td>
</tr>
<tr>
<td>3 R, severe</td>
<td>Diffuse infiltrate with multifocal myocyte damage. with or without edema, hemorrhage, or vasculitis</td>
</tr>
</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:**

Last accessed August 30, 2016.


Clinical Trials:

Searched clinicaltrials.gov on August 21, 2016 using terms “rejection,” “surveillance,” and “heart” | Open Studies. 3 studies found, 2 relevant.


CMS National Coverage Determination (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations

No LCDs 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.

<table>
<thead>
<tr>
<th>CPT Code</th>
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<tbody>
<tr>
<td>0085T</td>
<td>Heartsbreath</td>
<td></td>
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<tr>
<td>80180</td>
<td>Mycophenolate (mycophenolic acid)</td>
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<tr>
<td>86849</td>
<td>AllowMapDX, immunology procedure</td>
<td></td>
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<tr>
<td>93306</td>
<td>Echocardiography, transthoracic, real-time with image documentation</td>
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<table>
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<th>Description</th>
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<td>T86.20</td>
<td>Unspecified complication of heart transplant</td>
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<tr>
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<td>Heart transplant rejection</td>
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<tr>
<td>T86.22</td>
<td>Heart transplant failure</td>
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<td>T86.23</td>
<td>Heart transplant infection</td>
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<tr>
<td>T86.290</td>
<td>Cardiac allograft vasculopathy</td>
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<td>T86.298</td>
<td>Other complications of heart transplant</td>
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<td>T86.30</td>
<td>Unspecified complication of heart-lung transplant</td>
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<td>Encounter for aftercare following heart-lung transplant</td>
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<td>Heart transplant status</td>
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<td>Z94.3</td>
<td>Heart and lungs transplant status</td>
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