AlloMap Gene Expression Profiling for Heart Transplant Rejection

Introduction

AlloMap Gene Expression Profiling is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
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<td>AlloMap</td>
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What is AlloMap

Definition

AlloMap is a non-invasive blood test that is designed to help identify heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection at the time of testing.¹

Current uses

AlloMap is designed to help providers obtain this information without the use of endomyocardial biopsy. While endomyocardial biopsy is currently the standard of care for heart transplant recipients, it is an invasive procedure with associated risks.

Description

AlloMap is a panel of 20 genes. The assay uses gene expression of RNA isolated from peripheral blood mononuclear cells.¹

Results

Using data from the gene expression of these genes, an AlloMap score is calculated. The lower the score, the lower the probability of acute cellular rejection at the time of testing.¹
Intended use

AlloMap is intended for use in heart transplant recipients 15 years of age or older who are at least 2 months post heart transplant.¹

Test information

Introduction

The AlloMap assay measures the gene expression of RNA of 20 genes. 11 of these genes are thought to be informative for the assay, while the remaining 9 are used for quality control.¹

Risk score

The data collected from these genes is translated into a risk score. Scores range from 0-40 and are compared to post-transplant patients in the same post-transplant period. The lower the score, the lower the probability of acute cellular rejection at the time of testing.¹

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to AlloMap testing.

International Society of Heart and Lung Transplantation

The International Society of Heart and Lung Transplantation (2010)² stated the following:

“Gene Expression Profiling (AlloMap) can be used to rule out of the presence of acute cellular rejection (ACR) of grade 2R or greater in appropriate low risk patients, between 6 months and 5 years after HT.”

Class IIa

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Level of evidence: B – data derived from a single randomized clinical trial or large non-randomized studies.

U.S. Food and Drug Administration (FDA)

In 2008, the U.S. Food and Drug Administration (FDA) cleared AlloMap as a Class II Medical Device.³
EIMAGE (Early Invasive Monitoring Attenuation through Gene Expression)

The EIMAGE (Early Invasive Monitoring Attenuation through Gene Expression) study (2015)\(^4\) was conducted as a single-center randomized parallel 2-arm interventional study (n=60). This study compared AlloMap with heart biopsy in the first year post transplant.

- Study population consisted of 60 patients aged 18 years or older and at least 55 days post-transplant.
- Incidence of composite primary outcome in both groups was not statistically significant.
- The need for biopsy was reduced in the AlloMap monitoring group: 42 biopsies were performed in the AlloMap group vs. 253 in the biopsy group. 29 out of 42 of the biopsies performed in the AlloMap group were a direct result of the elevated AlloMap score.

IMAGE (Invasive Monitoring Attenuation through Gene Expression) study

The IMAGE (Invasive Monitoring Attenuation through Gene Expression) study (2010)\(^5\) serves as the first randomized, prospective trial (n=602) comparing AlloMap head-to-head with rejection monitoring by endomyocardial biopsy, the current standard of care. The study included patients who were clinically stable, 18 years of age or older, and at least 6 months post-transplant. Results of this study indicated:

- Rates of adverse events (primary outcome: rejection, graft dysfunction, death) were the same in low-risk patients monitored with AlloMap vs. traditional graft biopsy.
- The need for biopsy was reduced in the AlloMap monitoring group (since those with low scores did not get biopsies): 409 biopsies were performed in the AlloMap group vs. 1249 in the biopsy group.

However, limitations of this study were acknowledged by the authors. These limitations include:\(^5\)

- a study population that was likely significantly skewed toward patients at lower risk of rejection, since only patients who had received a cardiac transplant more than 6 months previously were eligible for enrollment
- wide statistical margins for comparing AlloMap vs. biopsy, and
- primary endpoint measures that included events that may not have been due to rejection.

The authors conclude that “gene expression profiling of peripheral blood specimens may offer a reasonable alternative to routine biopsies, for monitoring cardiac-transplant recipients for rejection if the interval since transplantation is at least 6 months and the patient is considered to be low risk for rejection.” \(^5\)
Crespo-Leiro et al

Crespo-Leiro et al (2015)\(^6\) conducted a study to examine the ability of AlloMap score variability to predict future events. They found that at a score variability of 0.6, the negative predictive value increased to 97% and the positive predictive value decreased to 23.3%. The authors concluded that “GEP score variability may be helpful in estimating probability of future events of death, re-transplantation or graft failure in heart transplant recipients.”

Deng et al

Deng et al (2014)\(^7\) conducted a study to examine the use of AlloMap score variability to predict clinical events in heart transplant recipients. They found that AlloMap score variability had a predictive accuracy of 0.69. They concluded, “the variability of gene expression profiling scores from an individual may help predict the risk of clinically defined future allograft dysfunction or death in the individual.”

Limitations of the Crespo-Leiro and Deng studies

These studies attempt to demonstrate the value of AlloMap scores for prognostic purposes. However, the studies are retrospective analyses of prospective studies and have notable limitations which marginalize their ability to effectively demonstrate clinical utility.

Criteria

Introduction

Requests for AlloMap Gene Expression Profiling are reviewed using the following criteria.

Criteria

This test is considered investigational and/or experimental.

- Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.
References

Introduction

These references are cited in this guideline.


