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Medical Policy Manual

Topic: Laboratory Tests for Heart Transplant Rejection

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

After heart transplantation, patients are monitored for cellular rejection by endomyocardial biopsies that are typically obtained from the right ventricle. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following 6 months, and several times (monthly to quarterly) between 6 months and 1-year post transplant. Surveillance biopsies may also be performed after the first postoperative year; e.g., on a quarterly or semi-annual basis. Due to the low rate of rejection after 1 year, some centers no longer routinely perform endomyocardial biopsies after a year in patients who are clinically stable.

Endomyocardial biopsy is invasive and carries significant risk of adverse effects. Additionally, while endomyocardial biopsy is considered the gold standard for assessing heart transplant rejection, biopsy may be limited by a high degree of interobserver variability in grading of results and the significant morbidity and even mortality that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy, and biopsy cannot be used to identify patients at risk of rejection, limiting the ability to initiate therapy to interrupt the development of rejection. For these reasons, endomyocardial biopsy is considered a flawed gold standard by many.

Therefore, noninvasive methods of detecting cellular rejection have been explored. It is hoped that noninvasive tests will assist in determining appropriate patient management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false-negative

and false-positive biopsy reports. Two techniques are commercially available for the detection of heart transplant rejection. The HeartsBreath™ test measures breath markers of oxidative stress, and the AlloMap® test provides gene expression profiling.

HeartsBreath Test

The Heartsbreath test (Menssana Research, Inc) is based on the understanding that in heart transplant recipients, oxidative stress appears to accompany allograft rejection. This rejection degrades membrane polyunsaturated fatty acids and evolving alkanes and methylalkanes, which are excreted as volatile organic compounds (VOC) in breath. The Heartsbreath test analyzes the breath methylated alkane contour (BMAC), which is derived from the abundance of C4 to C20 alkanes and monomethylalkanes.

AlloMap Test

Another approach, the AlloMap test (Xdx Inc.), focuses on patterns of gene expression of immunomodulatory cells as detected in the peripheral blood. For example, microarray technology permits the analysis of the gene expression of thousands of genes, including those with functions that are known or unknown. Patterns of gene expression can then be correlated with known clinical conditions, permitting a selection of a finite number of genes to compose a custom multi-gene test panel, which can then be evaluated using polymerase chain reaction (PCR) techniques. The test applies an algorithm to the results, which produces a single score that considers the contribution of each gene in the panel. The XDx website states that a lower score indicates a lower risk of graft rejection; the website does not cite a specific cut-off for a positive test.[1]

Additional Tests

Other laboratory-tested biomarkers of heart transplant rejection have been evaluated. These include brain natriuretic peptide, troponin, and soluble inflammatory cytokines. Most of these have had low diagnostic accuracy in diagnosing rejection.

Regulatory Status

Both the Heartsbreath and AlloMap tests have received approval from the US Food and Drug Administration (FDA):

- In 2004, the Heartsbreath test received approval from the FDA through a humanitarian device exemption. The Heartsbreath test is indicated for use as an aid in the diagnosis of grade 3 (significant) heart transplant rejection in patients who have received heart transplants within the preceding year. The test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. It is also limited to patients who have had endomyocardial biopsy within the previous month.
- AlloMap received 510k clearance from the FDA for use in conjunction with clinical assessment to identify heart transplant recipients with stable allograft function. The test is intended for patients at least 15 years-old who are at least 2 months post-transplant and who have a low probability of moderate/severe transplant rejection.

MEDICAL POLICY CRITERIA

I. The measurement of volatile organic compounds with the Heartsbreath test to assist in the detection of grade 3 heart transplant rejection is considered **investigational**.

II. The use of peripheral blood genetic profiling tests in the management of patients after heart transplantation, including but not limited to the detection of acute heart transplant rejection or heart transplant graft dysfunction, is considered **investigational**.

SCIENTIFIC EVIDENCE

The principal outcomes associated with detection of acute heart transplant rejection or graft dysfunction include hemodynamic compromise, graft dysfunction, and/or death. Outcomes relating to use of laboratory tests (currently limited to Heartsbreath or AlloMap) proposed for adjunctive use in heart transplant rejection are best understood by comparing outcomes of patients receiving endomyocardial biopsy alone to those receiving biopsy with the laboratory test. Data from adequately powered, blinded, randomized controlled trials (RCT) are required to control for baseline differences between groups and determine whether additional testing provides a significant advantage over the standard of care in any of the proposed uses of these laboratory tests.

Heartsbreath Test

A single non-randomized study was published in 2004 on the use of the Heartsbreath test. No subsequent studies that evaluate use of the Heartsbreath test to assess for graft rejection have been identified.

Nonrandomized Study

The FDA approval of the Heartsbreath test was based on the results of the National Heart Lung and Blood Institute-sponsored Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) study.[2] The HARDBALL study was a 3-year multicenter study of 1,061 breath samples in 539 heart transplantation patients. Prior to scheduled endomyocardial biopsy, patient breath was analyzed by gas chromatography and mass spectroscopy for VOCs. The amount of C4 to C20 alkanes and monomethylalkanes was used to derive the BMAC. The BMAC results were compared with subsequent biopsy results as interpreted by 2 readers using the International Society for Heart and Lung Transplantation biopsy grading system as the "gold standard" for rejection.

The authors of the HARDBALL study reported that the abundance of breath markers of oxidative stress were significantly greater in grades 0, 1 or 2 rejection than in healthy normal subjects. However, in grade 3 rejection, the abundance of breath markers of oxidative stress was reduced, most likely due to accelerated catabolism of alkanes and methylalkanes that comprised the BMAC. The authors also reported that in identifying grade 3 rejection, the negative predictive value of the breath test (97.2%) was similar to endomyocardial biopsy (96.7%), and that the breath test could potentially reduce the total number of biopsies performed to assess for rejection in patients at low risk for grade 3 rejection. The sensitivity of the breath test was 78.6%, versus 42.4% with biopsy. However, the breath test had lower specificity (62.4%) and a lower positive predictive value (5.6%) in assessing grade 3 rejection than

biopsy (specificity 97%, positive predictive value 45.2%). Additionally, the breath test was not evaluated in grade 4 rejection.

AlloMap Test

Several non-randomized studies, a randomized controlled trial and a technology assessment have been published on the use of the AlloMap test for monitoring of cardiac allograft rejection or graft dysfunction.

Technology Assessment

A 2011 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment was published on the utility of gene expression profiling (the AlloMap test was the only test under consideration) to monitor for cardiac allograft rejection.[3] The assessment addressed diagnostic accuracy and clinical utility and reached the following conclusions:

- Citing variability in the study methods (e.g., differing patient populations) and the lack of an established cut-off value for positive tests, the authors were not able to establish the diagnostic accuracy of the AlloMap test. In particular, test sensitivity remains poorly studied.

- Regarding evidence of clinical utility, the authors cited results from the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study (detailed below), which found equivalent health outcomes of patients monitored with AlloMap and biopsy versus biopsy alone. The TEC assessment therefore stated the current literature "does not provide strong evidence that AlloMap® testing is an effective strategy of rejection surveillance."

- Thus, the TEC assessment determined the available evidence was not sufficient to permit conclusions concerning the effects of gene expression profiling on health outcomes.

Randomized Controlled Trial (RCT)

- Results of the IMAGE study were published in 2010.[4,5] This was an industry-sponsored randomized controlled trial designed to test the non-inferiority of gene-expression profiling (the AlloMap test) compared to endomyocardial biopsies. Patients from 13 centers who underwent cardiac transplantation between 1 and 5 years previously, were clinically stable, and had a left ventricular ejection fraction (LVEF) of at least 45% were included. Each transplant center used its own protocol for determining the intervals for routine testing. Patients in both groups underwent clinical and echocardiographic assessments in addition to the assigned surveillance strategy. A total of 602 adult patients were randomly assigned to either the AlloMap test group (n=297) or the routine endomyocardial biopsy group (n=305).

  During a median follow-up period of 19 months, patients in the AlloMap group and the biopsy group had similar 2-year cumulative rates of the composite primary outcome (first occurrence o[f rejectio]n) (14.5% and 15.3%, respectively. The corresponding hazard ratio was 1.04 (95% confidence interval [CI]=0.67 to 1.68). The upper boundary of the CI of the hazard ratio, 1.68, fell within the prespecified non-inferiority margin (2.054). Thus, gene expression profiling was considered non-inferior to endomyocardial biopsy. However, because the overall survival rate did not differ significantly between the 2 groups (6.3% and 5.5%, respectively; P = 0.82), interpretation of test performance remains uncertain.

There were several limitations of the study. The threshold for a positive AlloMap test was changed part-way through the study; thus, the optimal test cut-off remains unclear. The study was not blinded, which could have impacted treatment decisions such as whether or not to recommend biopsy based on clinical findings. In addition, the study did not include a group that only received clinical and echocardiographic assessment and, therefore, the value of AlloMap testing beyond that of clinical management alone cannot be determined. The uncertain incremental benefit of the AlloMap test is highlighted by the finding that only 6 of the 34 (18%) treated episodes of graft rejection detected during follow-up in the AlloMap group were initially identified due solely to an elevated gene-profiling score. Finally, only 15% of the final study sample had undergone transplantation less than 1 year before study participation. Therefore, findings may not be generalizable to the population of patients 6 to12 months post-transplantation.

- An editorial accompanying the publication of the IMAGE study noted that an important implication of the trial was that it called into question the need for any type of long-term routine screening for early transplant rejection.[6] Some centers reached the conclusion that clinical outcomes may not be substantially worse when rejection is not detected early; they stopped performing routine endomyocardial biopsies between 1 and 5 years' post transplantation.

Nonrandomized Studies

- Patterns of gene expression were studied in the Cardiac Allograft Rejection Gene Expression Observation Study (CARGO) study, which included 8 US cardiac transplant centers enrolling 650 cardiac transplant recipients, encompassing over 5,000 clinical encounters. Patient blood samples were obtained at the time of endomyocardial biopsy, and the expression levels of over 7,000 genes known to be involved in immune responses were assayed and compared to the biopsy results. A subset of 200 candidate genes were identified that showed promise as markers that could distinguish transplant rejection from quiescence, and from there, a panel of 20 genes was selected that could be evaluated using PCR assays. A proprietary algorithm was applied to the results of the analysis producing a single score that considered the contribution of each gene in the panel. The third phase in the development of the AlloMap test was a pivotal validation study designed to further evaluate the algorithm and establish performance characteristics of the test. This phase of the study, which enrolled 270 patients, was prospective and blinded.

  Results of the CARGO study were published in 2006.[7-11] Primary validation was conducted using samples from 63 patients independent from discovery phases of the study and enriched for biopsy-proven evidence of rejection. A prospectively defined test cutoff value of 20 resulted in correct classification of 84% of patients with moderate/severe rejection but just 38% of patients without rejection. The authors evaluated the 11-gene expression profile on 281 samples collected at 1 year or more from 166 patients' representative of the expected distribution of rejection in the target population (and not involved in the discovery or validation phases of the study). When a test cutoff of 30 was used, the negative predictive value (no moderate/severe rejection) was 99.6%; however, only 3.2% of specimens had grade 3 or higher rejection. In this population, grade 1B scores were found to be significantly higher than grade 0, 1A, and 2 scores, but were similar to grade 3 scores. The sensitivity and specificity for determining quiescent versus early stages of rejection was not addressed.

- Post-CARGO clinical observations have been published.[12] The multicenter work group identified a number of factors that can affect AlloMap scores, including the post-transplantation time,

corticosteroid dosing, and transplant vasculopathy.[12,13] Scores of 34 and above were considered positive, potentially indicating rejection, whereas scores below that threshold were considered negative with no evidence of rejection. Analysis of data from a number of centers collected post-CARGO showed that, at 1 year or more post-transplantation, an AlloMap threshold of 34 had a positive predictive value of 7.8% for scores of ≥ 3A/2R on biopsy and a negative predictive value of 100% for AlloMap scores below 34. These findings were limited due to a very low number of events; only 5 biopsy samples (2.4%) were found to have a grade of 2R or greater. At 1 year, 28% of the sample showed an elevated AlloMap score (>34) even though there was absence of evidence of rejection on biopsy. The significance of chronically elevated AlloMap scores in the absence of clinical manifestation of graft dysfunction and the actual impact on the number of biopsies performed is currently unknown.

- In a follow-up analysis of data from the IMAGE RCT, Deng et al evaluated whether variability in gene expression profiling results were predictive of clinical outcomes.[14] For this analysis, the authors included a subset of 369 patients who had at least 2 AlloMap tests done before an event or the study end, and at least 1 endomyocardial biopsy and 1 echocardiogram. Patients were included from both arms of the IMAGE RCT. AlloMap test results were expressed in 3 ways, as an ordinal score from 0 to 39, a threshold score of 1 or 0 depending on whether the score was 34 or more or not, and as a variability score, the standard deviation of all of the ordinal scores within a patient. The AlloMap results were entered into a multivariable regression model to predict the composite end point, defined as a patient's first occurrence of: rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. AlloMap ordinal score and AlloMap threshold score were not predictive of the composite outcome. AlloMap score variability was significantly associated with the composite outcome, with a hazard ratio for a 1-unit increase in variability of 1.76 (95% CI, 1.4 to 2.3). Authors concluded the variability of a heart recipient's gene expression profiling test scores over time may provide prognostic utility.

In sum, the studies examining the diagnostic performance of AlloMap testing for detecting moderate/severe rejection are flawed by lack of a consistent threshold for determining positivity and very small sample sizes. The studies that examined cutoff scores of 30 or 34, calculated sensitivities of 80-100%, based on detecting 10 or fewer cases of rejection in each of 3 studies.[3]

Clinical Practice Guidelines

No evidence-based clinical practice guidelines have been identified which recommend the use of any type of laboratory test for the detection of heart transplant rejection.

In 2010, the International Society of Heart and Lung Transplantation issued consensus-based guidelines for the care of heart transplant recipients.[15] The guidelines included the following recommendations:

- The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy during the first 6 to 12 months after transplant for rejection surveillance.
- After the first year post-transplant, endomyocardial biopsy surveillance every 4 to 6 months is recommended for patients at higher risk of late acute rejection.
- Gene Expression Profiling using the AlloMap test can be used to rule out acute heart rejection (grade 2 or greater) in appropriate low-risk patients between 6 months and 5 years post-transplant.

Summary

There is insufficient evidence on the diagnostic accuracy of the Heartsbreath test, especially for grades 3 and 4 rejection. There are no studies that address the clinical utility, or how patient management changes, as a result of the Heartsbreath test. Therefore, use of the Heartsbreath test to assist in the detection of heart transplant rejection is considered investigational.

While there is evidence on the diagnostic accuracy of the AlloMap test, the evidence is not sufficiently rigorous to estimate the true sensitivity and specificity of the test with any level of certainty. In addition, there is insufficient evidence on the clinical utility, or how patient management changes as a result of AlloMap results. Thus, use of the AlloMap test to assist in the detection of heart transplant rejection is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	0085T	Breath test for heart transplant rejection
	86849	Unlisted immunology procedure
HCPCS	None	