05-86000-24

Original Effective Date: 03/15/05

Reviewed: 12/05/19

Revised: 01/15/20

Subject: Laboratory Tests for Heart and Kidney Transplant Rejection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CEbRTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Acute cellular rejection is most likely to occur in the first six months after transplantation, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a life-long basis, dosing is adjusted based on graft function and the grade of acute cellular rejection determined by histopathology. Endomyocardial biopsies are typically taken periodically during the first 6 to 12 months post-transplant. The interval between biopsies varies among clinical centers. A typical schedule is weekly for the first month, once or twice monthly for the following six months, and several times (monthly to quarterly) between six months and one year post-transplant. Surveillance biopsies may also be performed after the first postoperative year (eg, on a quarterly or semiannual basis). This practice, although common, has not been demonstrated to improve transplant outcomes. Some centers no longer routinely perform endomyocardial biopsies after one year in patients who are clinically stable.

While the endomyocardial biopsy is the criterion standard for assessing heart transplant rejection, it is limited by a high degree of interobserver variability in the grading of results and potential morbidity that can occur with the biopsy procedure. Also, the severity of rejection may not always coincide with the grading of the rejection by biopsy. Finally, a 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, an endomyocardial biopsy is considered a flawed criterion standard by many.

Noninvasive methods of detecting cellular rejection have been explored with the hope 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-negativeand false-positive biopsy reports.

Several commercially available laboratory tests assess heart transplant rejection, including the Heartsbreath test, which measures breath markers of oxidative stress, and the AlloMap test, which uses gene expression profiling. These tests create a score based on the expression of a variety of immunomodulatory genes and are proposed as an alternative or as an adjunct to invasive endomyocardial biopsy. Renal transplant rejection may be assessed by the AlloSure test, which measures the donor-derived cell-free DNA in peripheral blood and is proposed as an alternative or as an adjunct to invasive renal biopsy. A protein biomarker, soluble suppression of tumorigenicity-2 (sST2), has also elicited interest as a prognostic marker post heart transplantation and as a test to predict acute cellular rejection (graft-versus-host disease).

POSITION STATEMENT:

AlloMap® molecular expression testing **meets the definition of medical necessity** as a non-invasive method of determining the risk of rejection in heart transplant recipients (15 years or older) who are between 6 months and 5 years post-transplant.

AlloMap molecular expression testing is considered **experimental or investigational** for all other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

The use of all other molecular expression tests in the management of members after heart transplantation is considered **experimental or investigatioinal**. The evidence is insufficient to determine the effects of the technology on health outcomes.

The measurement of volatile organic compounds (e.g. Heartsbreath® test) to assist in the detection of moderate grade 2R (formerly grade 3) heart transplant rejection is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

The use of peripheral blood measurement of donor-derived cell-free DNA in the management of members after renal transplantation, including but not limited to the detection of acute renal transplant rejection or renal transplant graft dysfunction (e.g. AlloSure®) is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

The use of the Presage® ST2 assay is considered **experimental or investigational** for all indications including, but not limited to, predicting prognosis and predicting acute cellular rejection in the post cardiac transplantation period. The evidence is insufficient to determine the effects of the technology on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

81595	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
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1) (**Investigational**)
0085T	Breath test for heart transplant rejection (**Investigational**)
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma

	(**Investigational**)
0087U	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score (**Investigational**)
0088U	Transplantation medicine (kidney allograft rejection) microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection (**Investigational**)
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA (**Investigational**)

ICD-10 Diagnosis Codes That Support Medical Necessity for 81595:

T86.20-T86.298	Complications of heart transplant
Z48.21	Encounter for aftercare following heart transplant
Z94.1	Heart transplant status

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products:

The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Heartsbreath Test for Heart Transplant Rejection (260.10) located at cms.gov.

The following was reviewed on the last guideline reviewed date and located at palmettogba.com:

- Local Coverage Article:MolDX:AlloMap Billing and Coding Guidelines Update (A53099)
- Local Coverage Determination (LCD):MolDX: AlloSure® Donor-Derived Cell-Free DNA Test (L37266).

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

REFERENCES:

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3. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.130 ST2 Assay for Chronic Heart Failure and Heart Transplant Rejection, 06/19.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy & Coverage Committee on 12/05/19.

GUIDELINE UPDATE INFORMATION:

03/15/04	New Medical Coverage Guideline.
03/15/06	Annual review; continue investigational status.
03/15/07	Scheduled review; no change in coverage statement; references.
06/15/07	Reformatted guideline.
11/15/07	Revision: title changed, description section updated, position statement updated, Medicare Advantage section updated, references updated.
02/15/08	Annual review: position statements maintained; description section updated; references updated.
02/15/09	Annual review: position statements maintained; description section and references updated.
12/15/09	Annual review: position statements maintained; description section and references updated.
09/15/12	Review; position statements maintained; program exceptions section and references

	updated.
06/15/13	Annual review; position statements maintained and references updated.
06/15/14	Annual review; position statements maintained, program exception and reference updated.
06/15/15	Annual review; position statements maintained and references updated.
01/01/16	Annual HCPCS/CPT update; code 81595 added.
07/15/16	Annual review; revise the position statement section, coding, program exception, and references.
12/15/17	Annual review; investigational position maintained; description, position statements, and references updated.
12/15/18	Annual review; Investigational position maintained; investigational statement for AlloSure test added; title, description, coding, and references updated.
07/01/19	Quarterly CPT/HCPCS update. Added codes 0087U & 0088U.
01/15/20	Review; position statements, coding, description, and references updated.