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Genetic Testing for Organ Transplantation

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Scope

This evidence-based guideline addresses molecular testing for organ transplantation.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature.

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

HLA typing and chimerism testing is medically necessary for all transplant indications.

The use of gene expression profiling, i.e., AlloMap®, for post-transplant heart rejection monitoring is medically necessary when all of the following criteria are met:

- individual is ≥15 years of age
- individual is two months to five years post-transplant
- stable heart allograft function is demonstrated at the time of testing with no signs of heart failure
- low probability of moderate or severe rejection exists at the time of testing

The use of AlloMap® for any other indication is considered never medically necessary.

All other non-invasive molecular tests to monitor allograft rejection are considered never medically necessary including donor-derived cell-free DNA (dd-cfDNA) monitoring, other gene expression profile tests or a combination of these testing methodologies.

Key Terms and Definitions

Allograft rejection occurs when the recipient's immune system recognizes and attacks a transplanted organ or tissue (allograft) as foreign.
Chimerism testing refers to genetic testing to determine the proportion of donor and recipient cells in an individual's body post transplant, in order to monitor the success of the transplant and detect any complications.
Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.
Donor-derived cell-free DNA (dd-cfDNA) is a type of genetic material that originates from a transplanted donor organ or tissue and circulates in the bloodstream of the organ recipient.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Gene expression profile refers to the pattern of gene activity or expression levels in a given cell or tissue sample at a specific time; this provides a snapshot of which genes are being actively transcribed and their associated levels of protein production or cellular activity.
Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.
HLA (human leukocyte antigen) typing is used to determine compatibility between donors and recipients by matching individuals with compatible HLA markers.
Non-invasive molecular tests typically involve less burdensome and non-invasive alternatives to traditional tissue biopsies in order to obtain and evaluate biological samples, such as DNA.
Ribonucleic acid (RNA) is a molecule that plays a crucial role in various cellular processes within living organisms, such as cell functioning and regulation.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by

a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following list of code(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Full Description
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample]
81267	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type
81370	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
81371	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)
81372	HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
81373	HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each
81374	HLA Class I typing, low resolution (eg, antigen equivalents); one antigen equivalent (eg, B*27), each
81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377	HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81382	HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81383	HLA Class II typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, HLA-DQB1*06:02P), each
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

The following code(s) are considered never medically necessary. This list is not all inclusive.

Code	Full Description
81558	Transplantation medicine (allograft rejection, kidney), mRNA, gene expression profiling by quantitative polymerase chain reaction (qPCR) of 139 genes, utilizing whole blood, algorithm reported as a binary categorization as transplant excellence, which indicates immune quiescence, or not transplant excellence, indicating subclinical rejection
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma
0087U	Tissue rejection (allograft organ heart), mRNA gene expression analysis of 1,283 genes utilizing microarray, measuring mRNA transcript levels in transplant heart biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
0088U	Tissue rejection (allograft organ kidney), mRNA gene expression analysis of 1,494 genes utilizing microarray, measuring mRNA transcript levels in transplant kidney biopsy tissue, with allograft rejection and injury algorithm reported as a probability score
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
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection
0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using post transplant peripheral blood, algorithm reported as a risk score for acute cellular rejection
0493U	Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA
0508U	Transplantation medicine, quantification of donor-derived cell-free DNA using 40 single- nucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cell-free DNA with risk for active rejection
0509U	Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection
0540U	Transplantation medicine, quantification of donor derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection
0544U	Nephrology (transplant monitoring), 48 variants by digital PCR, using cell-free DNA from plasma, donor-derived cell-free DNA, percentage reported as risk for rejection

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

NCCI Policy Manual for Medicare Services. Available at: https://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd. Accessed quarterly.

NCCI Policy Manual for Medicaid Services. Available at: https://www.medicaid.gov/medicaid/program-integrity/national-correct-coding-initiative/medicaid-ncci reference-documents/index.html

Organ Transplantation

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable
v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC: 8/16/2023 PAB: 9/25/2023	October 1, 2023	Semi-annual review. No criteria changes.
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. Coverage criteria for AlloMap was expanded to allow testing for individuals two months to five years post-transplant. Clarifications were made to the scope and CPT code sections. References were updated.
v2.2024	COOC: 08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. CPT codes were updated.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. No criteria changes. CPT codes updated.