

# Molecular Pathology Procedures for Human Leukocyte Antigen (HLA) Typing

**LCD ID** L34943

## **Jurisdiction**

Tennessee

## **Original Effective Date**

For services performed on or after 10/01/2015

## **LCD Title**

Pathology and Laboratory: Molecular Pathology Procedures for Human Leukocyte Antigen (HLA) Typing

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## **CMS National Coverage Policy**

- Title XVIII of the Social Security Act, Section 1833(e). This section states that no payment shall be made to any provider for any claims that lack the necessary information to process the claim.
- Title XVIII of the Social Security Act, Section 1862(a)(1)(A). This section allows coverage and payment for only those services that are considered to be reasonable and medically necessary, i.e., reasonable and necessary are those tests used in the diagnosis and management of illness or injury or to improve the function of a malformed body part.
- Title XVIII of the Social Security Act, Section 1862(a)(1)(D). Investigational or Experimental.
- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations and services.
- 42 CFR Section 410.32(a) indicates diagnostic tests are payable only when the physician who is treating the beneficiary for a specific medical problem uses the results in such treatment.
- Medicare Benefit Policy Manual (Pub.100-02), Chapter 15, Sections 80.1, 80.1.1, 80.1.2, 80.1.3.
- Medicare National Coverage Determinations Manual (Pub. 100-03), Chapter 1, Part 3, Section 190.1. Histocompatibility Testing.
- Medicare Program Integrity Manual (Pub. 100-08), Chapter 13.

## Coverage Guidance

### Coverage Indications, Limitations, and/or Medical Necessity

#### **Background**

Human Leukocyte Antigen (HLA) typing is performed to assess compatibility of recipients and potential donors as a part of solid organ and hematopoietic stem cell/ bone marrow pre-transplant testing. HLA testing is also performed to identify HLA alleles and allele groups (antigen equivalents) associated with specific diseases and individualized responses to drug therapy (e.g., HLA-B\*27 and ankylosing spondylitis and HLA-B57:01 and abacavir hypersensitivity), as well as other clinical uses. One or more HLA genes may be tested in specific clinical situations (e.g., HLA A, B, C,-DRB1, and DQB1 for kidney transplantation). Each HLA gene typically has multiple variant alleles or allele groups that can be identified by typing.

HLA antigens are divided into types: Class I (A, B, C) and Class II (DR, DP, DQ). The primary use for HLA testing is to match organ and tissue transplant recipients with compatible donors. Different kinds of transplants necessitate different levels of matching between donor and intended recipient. This may determine which HLA tests are performed and which HLA genes are tested for. HLA typing identifies the unique constellation of HLA antigens for an individual.

HLA typing using newer DNA technologies provides tests that are more robust, accurate and reliable in resolving allele-level differences in HLA genes that cannot be detected by serology. DNA tests can be performed using a variety of source materials (lymphocytes, whole blood, buccal swabs, biopsy samples, frozen tissue) and are less affected by viability and sample age. Several approaches to HLA typing are used, offering a range of typing resolution levels from low (antigen-level) to high (allele-level). Examples include, tests used to identify HLA types that rely on amplification of limited stretches of genomic DNA within the HLA genes. The genetic polymorphisms associated with the different HLA alleles are identified through hybridization with specific amplification primers: sequence-specific primer (SSP) or sequence specific oligonucleotide probes (SSO) or by direct sequencing-based typing (SBT).

#### **PCR-SSO**

Reverse SSO hybridization is used to determine HLA-A, -B, -C, -DR, -DQ and -DP locus types at an intermediate level of resolution, somewhat higher than serological testing. Tests of this type are used when low or intermediate resolution typing is required or as a screening test to identify potential donors or individuals who may later require higher resolution testing.

This technology is used for high volume testing and allows for relatively low-cost typing for bone marrow donor drives or other applications involving large sample numbers.

#### **PCR-SSP**

PCR-SSP is also used to determine HLA-DP and to determine, at a resolution similar to serological testing, HLA-A, -B, -C, -DR and DQ locus types. PCR-SSP is a very rapid test that can be performed in 3-4 hours from the time a sample is received. PCR-SSP is used for typing deceased organ donors when speed is an important consideration. PCR-SSP can also be used to provide higher resolution testing and may be employed to resolve alleles. In this technique, PCR primers are designed to anneal only to a specific set of alleles or to a single allele.

#### **SBT**

SBT provides the highest resolution HLA typing for HLA-A, -B, -C, -DR, -DQ and -DP locus alleles. SBT is

used when the highest resolution typing is important as in donors and recipients of stem cell transplants or in examining disease associations.

### **Indications**

The commercial availability does not ensure that a molecular diagnostic test is indicated for clinical application. Molecular diagnostic testing is a rapidly evolving science in which the significance of detecting specific mutations has yet to be clarified in many circumstances. Analytical and clinical validity as well as clinical utility are the responsibility of the provider, and all testing must meet standards of care.

For the purpose of this LCD, the Molecular Pathology Procedures for HLA typing will be considered medically and reasonable necessary when the following apply:

1. Transplantation:
  - A. Standard of care determination of HLA matching for solid organ transplant (donor/recipient). Solid organ transplant registries include both serological HLA testing (e.g. crossmatch) and genomic molecular DNA typing. Family members, or unrelated living donors or cadaveric donors who donate bone marrow or a solid organ are HLA tested pretransplant to determine compatibility with the potential recipients.
  - B. Standard of care identification of determination of HLA matching for hematopoietic stem cell/bone marrow transplantation. Allele-level typing will provide clinical guidance for the HLA-A,B,C Class I and DRB1, DQB1,DPB1, and DQA1 Class II loci in the average transplant program because it is well established that mismatches at certain HLA loci between donor-recipients are closely linked to the risk of graft versus host disease. Potential marrow donors may enroll with a national registry such as the United States National Marrow Donor Program or the Canadian Blood Services registry.
2. Disease Association:
  - A. Standard of care testing to diagnose certain HLA related diseases/conditions when the testing is supported by the clinical literature and is informative for the direct management of a patient bearing a certain allele(s). It is not expected that more than one test would be required in a given beneficiary's lifetime. Possible covered indications when standard laboratory testing (tissue typing) is not adequate:
    - i. HLA-B\*27 for the diagnosis of certain cases of symptomatic patients with presumed ankylosing spondylitis or related inflammatory disease. HLA-B\*27 is covered for ankylosing spondylitis in cases where other methods of diagnosis would not be appropriate or have yielded inconclusive results (National Coverage Determination 190.1).
    - ii. In the work-up of certain patients with an unclear diagnosis of celiac disease and gluten hypersensitivity usually related to ambiguous standard laboratory results and/or inconsistent biopsy results (e.g., HLA-DQ2 by HLA-DQB1\*02 and of DQ8 by HLA-DQB1\*0302).
3. Pharmacogenetics:
  - A. Standard of care testing to diagnose certain HLA related drug hypersensitivity reactions when the testing is supported by the clinical literature and is informative for the direct management of a patient bearing a certain allele(s) associated to fatal skin drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis). It is not expected that more than one test would be required in a given beneficiary's lifetime. Possible covered indications:
    - i. HLA –B\*5701 when testing performed prior to the initiation of an abacavir-containing regime in the treatment of HIV Infection.
    - ii. HLA-B\*1502 when genotyping may be useful for risk stratification when the testing is performed prior to the initiation of carbamazepine therapy in the treatment of patients at high

risk of having this allele. HLA-B\*1502 occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.

4. Identification of HLA compatible platelets for transfusion.

### **Limitations**

The following will be considered noncovered as applicable due to statutory exclusion, lack of Medicare benefit, not reasonable and necessary, or not separately billable (a component of the service per NCCI regulations).

1. Tests considered screening in the absence of clinical signs and symptoms of disease (e.g., HLA-DQB1\*06:02P as a positive/negative predictor for narcolepsy).
2. Tests that do not provide the clinician with actionable data (information that will improve patient outcomes and/or change physician care and treatment of the patient).
3. Tests that confirm a known diagnosis or known information (and no new data for decision making).
4. Tests to determine risk for developing a disease or condition.
5. Tests without diagnosis specific indications.
6. Tests performed to measure the quality of a process.
7. Tests for Quality Control/Quality Assurance (QC/QA), i.e., tests performed to ensure a tissue specimen matches the patient.
8. Tests assessing the risk of allopurinol hypersensitivity reactions (HLA-B\*58:01P).

## Coding Information

### **Bill Type Codes:**

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type.

Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

### **Revenue Codes:**

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination.

Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

### **CPT/HCPCS Codes**

**Group 1 Paragraph:** N/A

**Group 1 Codes:**

81370	Hla i & ii typing lr
81371	Hla i & ii type verify lr
81372	Hla i typing complete lr
81373	Hla i typing 1 locus lr
81374	Hla i typing 1 antigen lr
81375	Hla ii typing ag equiv lr
81376	Hla ii typing 1 locus lr
81377	Hla ii type 1 ag equiv lr
81378	Hla i & ii typing hr
81379	Hla i typing complete hr
81380	Hla i typing 1 locus hr
81381	Hla i typing 1 allele hr
81382	Hla ii typing 1 loc hr
81383	Hla ii typing 1 allele hr

**ICD-10 Codes that Support Medical Necessity**

**Group 1 Paragraph:** The correct use of an ICD-10-CM code listed in the “ICD-10 Codes that Support Medical Necessity” section does not guarantee coverage of a service. The service must be reasonable and necessary in the specific case and must meet the criteria specified in this LCD.

ICD-10 codes must be coded to the highest level of specificity. Consult the ‘Official ICD-10-CM Guidelines for Coding and Reporting’ in the current ICD-10-CM book for correct coding guidelines. This LCD does not take precedence over the Correct Coding Initiative (CCI).

**CPT Codes 81370-81383****CPT Codes 81370-81383****Group 1 Codes:**

Group 1Codes	
ICD-10 CODE	DESCRIPTION
<a href="#">T86.00 - T86.819- Opens in a new window</a>	Unspecified complication of bone marrow transplant - Unspecified complication of lung transplant

<a href="#">T86.830 - T86.839- Opens in a new window</a>	Bone graft rejection - Unspecified complication of bone graft
<a href="#">T86.850 - T86.99- Opens in a new window</a>	Intestine transplant rejection - Other complications of unspecified transplanted organ and tissue
<a href="#">Z48.21 - Z48.298- Opens in a new window</a>	Encounter for aftercare following heart transplant - Encounter for aftercare following other organ transplant
<a href="#">Z94.0 - Z94.9- Opens in a new window</a>	Kidney transplant status - Transplanted organ and tissue status, unspecified
<a href="#">Z95.3 - Z95.4- Opens in a new window</a>	Presence of xenogenic heart valve - Presence of other heart-valve replacement

**Group 2 Paragraph: CPT Code 81374 for HLA-B\*27 Testing**

**Group 2 Codes:**

Group 2Codes	
ICD-10 CODE	DESCRIPTION
M08.1	Juvenile ankylosing spondylitis
<a href="#">M45.0 - M45.9- Opens in a new window</a>	Ankylosing spondylitis of multiple sites in spine - Ankylosing spondylitis of unspecified sites in spine
<a href="#">M48.8X1 - M48.8X9- Opens in a new window</a>	Other specified spondylopathies, occipito-atlanto-axial region - Other specified spondylopathies, site unspecified

**Group 3 Paragraph: CPT code 81381 for HLA-B\*1502 Testing**

**Group 3 Codes:**

Group 3Codes	
ICD-10 CODE	DESCRIPTION
<a href="#">R56.00 - R56.9- Opens in a new window</a>	Simple febrile convulsions - Unspecified convulsions
Z79.3*	Long term (current) use of hormonal contraceptives

Z79.891\*

Long term (current) use of opiate analgesic

Z79.899\*

Other long term (current) drug therapy

**Group 3 Medical Necessity ICD-10 Codes Asterisk Explanation: \*Must also be reported with each primary diagnosis code. This is a dual diagnosis requirement.**

**Group 4 Paragraph: CPT code: 81381 for HLA-B\*5701 Testing**

**Group 4 Codes:**

#### Group 4 Codes

ICD-10 CODE	DESCRIPTION
B20	Human immunodeficiency virus [HIV] disease
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

**Group 5 Paragraph: CPT codes 81376, 81377, 81382, and 81383**

**Group 5 Codes:**

#### Group 5 Codes

ICD-10 CODE	DESCRIPTION
K90.0	Celiac disease

## General Information

### Associated Information

### Documentation Requirements

1. All 'Indications' must be clearly documented in the patient's medical record and made available to Medicare upon request.

2. The laboratory or billing provider must have on file the physician requisition which sets forth the diagnosis or condition (ICD-9-CM code) that warrants the test(s).
3. When the documentation does not meet the criteria for the services rendered, or the documentation does not establish the medical necessity for the services, such services will be denied as not reasonable and necessary under Section 1862(a)(1) of the Social Security Act.
4. Documentation must support CMS 'signature requirements' as described in the Medicare Program Integrity Manual (Pub. 100-08), Chapter 3.

### Utilization Guidelines

Screening services, such as pre-symptomatic genetic tests and services used to detect an undiagnosed disease or disease predisposition are not a Medicare benefit and not covered.

### Sources of Information and Basis for Decision

- American Medical Association. Current Procedural Terminology CPT®2013 Professional Edition. Chicago, IL: AMA, 2012.
- [ASHI Quarterly- Fourth Quarter 2010](#) . HLA Alleles and Drug Hypersensitivity Reactions.
- [ARUP National Laboratories](#) . Ankylosing Spondylitis Genotyping (HLA-B27).
- Chao J and Terkeltaub R. A Critical Reappraisal of Allopurinol Dosing, Safety, and Efficacy for Hyperuricemia in Gout. Current Rheumatology Reports 2009, 11:135–140
- Consultations with the representatives to the Carrier Advisory Committee and other Medicare Contractors.
- Ferrell PB, McLeod HL. Carbamazepine, HLA-B\*1502 and Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: US FDA Recommendations. Pharmacogenomics 2008 Oct;9(10):1543-6
- [Lab Tests Online](#).
- Mallal S, Phillips E, Carosi G. HLA-B\*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008; 358:568-579.
- Nakayama J, Miura M, Honda M, et al. Linkage of human narcolepsy with HLA association to chromosome 4p13-q21. Genomics 2000 Apr 1;65(1):84-6
- [Nanosphere](#). Nanosphere Receives FDA Clearance to Market Test for Detection of CYP2C19 Mutations Affecting Drug Metabolism.
- Other Medicare Contractor's Local Coverage Determinations.
- [Quest Diagnostics](#). HLA Test Menu.
- [UCLA Immunogenetics Center](#).
- [U.S. Food and Drug Administration](#). Information on Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics).

## Local Coverage Determination (LCD) Disclaimer

The Centers for Medicare & Medicaid Services (CMS), the federal agency responsible for administration of the Medicare, Medicaid and the State Children's Health Insurance Programs, contracts with certain organizations to assist in the administration of the Medicare program. Medicare contractors are required to develop and disseminate Local Coverage Determinations (LCDs). CMS believes that the Internet is an effective method to share LCDs that Medicare contractors develop. While every effort has been made to provide accurate and complete information, CMS does not guarantee that there are no errors in the information displayed on this web site. THE UNITED STATES GOVERNMENT AND ITS EMPLOYEES ARE NOT LIABLE FOR ANY ERRORS, OMISSIONS, OR OTHER INACCURACIES IN THE INFORMATION, PRODUCT, OR PROCESSES DISCLOSED HEREIN. Neither the United States Government nor its employees represent that use of such information, product, or processes will not

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