

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

CPT: 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378,  
81379, 81380, 81381, 81382, 81383

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

As outlined in the CPT Molecular Pathology procedures sections, 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 pretransplant 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.

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### 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: 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. 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: 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) not adequate: 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 (NCD 190.1). 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: 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:  
HLA –B\*5701 when testing performed prior to the initiation of an abacavir-containing regime in the treatment of HIV Infection.  
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 when standard typing is not adequate.

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## Limitations

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

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)

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)

Tests that confirm a known diagnosis or known information (and no new data for decision making)

Tests to determine risk for developing a disease or condition

Tests without diagnosis specific indications

Tests performed to measure the quality of a process

Tests for Quality Control/Quality Assurance (QC/QA), i.e., tests performed to ensure a tissue specimen matches the patient

Tests assessing the risk of allopurinol hypersensitivity reactions (HLA-B\*58:01P)

# Human Leukocyte Antigen (HLA) Typing

## HLA-B\*27

CPT: 81374

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The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**

**\*Note—Bolded diagnoses below have the highest utilization**

Code	Description
M08.1	Juvenile ankylosing spondylitis
M45.0	Ankylosing spondylitis of multiple sites in spine
M45.1	Ankylosing spondylitis of occipito-atlanto-axial region
M45.2	Ankylosing spondylitis of cervical region
M45.3	Ankylosing spondylitis of cervicothoracic region
M45.4	Ankylosing spondylitis of thoracic region
M45.5	Ankylosing spondylitis of thoracolumbar region
M45.6	Ankylosing spondylitis lumbar region
M45.7	Ankylosing spondylitis of lumbosacral region
M45.8	Ankylosing spondylitis sacral and sacrococcygeal region
M45.9	Ankylosing spondylitis of unspecified sites in spine
M48.8X1	Other specified spondylopathies, occipito-atlanto-axial region
M48.8X2	Other specified spondylopathies, cervical region
M48.8X3	Other specified spondylopathies, cervicothoracic region
M48.8X4	Other specified spondylopathies, thoracic region
M48.8X5	Other specified spondylopathies, thoracolumbar region
M48.8X6	Other specified spondylopathies, lumbar region
M48.8X7	Other specified spondylopathies, lumbosacral region
M48.8X8	Other specified spondylopathies, sacral and sacrococcygeal region
M48.8X9	Other specified spondylopathies, site unspecified

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Last updated: 04/2023

#### Disclaimer:

This diagnosis code reference guide is provided as an aid to physicians and office staff in determining when an ABN (Advance Beneficiary Notice) is necessary. Diagnosis codes must be applicable to the patient's symptoms or conditions and must be consistent with documentation in the patient's medical record. Quest Diagnostics does not recommend any diagnosis codes and will only submit diagnosis information provided to us by the ordering physician or his/her designated staff. The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

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# Human Leukocyte Antigen (HLA) Typing

## HLA-B\*5701

CPT: 81381

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Code	Description
<b>B20</b>	<b>Human immunodeficiency virus [HIV] disease</b>
<b>Z21</b>	<b>Asymptomatic human immunodeficiency virus [HIV] infection status</b>

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# Human Leukocyte Antigen (HLA) Typing

## HLA-B\*1502

CPT: 81381

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Code	Description
R56.00	Simple febrile convulsions
R56.01	Complex febrile convulsions
R56.1	Post traumatic seizures
R56.9	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

**\* Diagnosis codes Z79.3, Z79.891 and/or Z79.899 must also be reported with each primary diagnosis code. This is a dual diagnosis requirement**

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CPT: 81376, 81377, 81382, 81383

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Code	Description
<b>K90.0</b>	<b>Celiac disease</b>

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