



REQUEST FOR MOLECULAR PATHOLOGY CODE REVIEW AND FEEDBACK

Key Points

- In December 2009, the AMA CPT® Editorial Panel convened a workgroup to propose solutions to issues for coding molecular assays in cancer, genetics and histocompatibility.
- The output of that workgroup illustrated in the test descriptors provided and available in this release for review and comment to interested stakeholders before publication for CPT 2012 represents the major changes to molecular assay reporting that are coming next year.
- These changes do NOT affect molecular microbiology tests or most cytogenetic assays.
- The most commonly-performed tests (Tier 1) will have a test (analyte) specific CPT code.
- Less commonly-performed tests (Tier 2) have been assigned to 9 resource level codes determined by level of resources required for their performance and interpretation.
- Analytes/tests that have new codes assigned and are listed in Tiers 1 and 2 MUST be coded using the most specific CPT code available and NOT with 'stacking codes' (83890-83914).
- CPT 'stacking codes' (83890-83914) will remain available to report tests in 2012 for tests that have not been assigned Tier I/Tier II analyte-specific or resource level codes. 'Stacking codes' will be retired at the conclusion of this initiative (most likely 2013), after which an unlisted code will be developed to report tests without specific analyte or resource level codes.

Review and Feedback

In response to the concerns raised by multiple payers and providers, the CPT® Editorial Panel Molecular Pathology Coding Workgroup (MPCW) was convened in December 2009 with the charge to construct a new subsection of the CPT Pathology and Laboratory subsection, guidelines, definitions and new CPT codes. The molecular infectious agent codes were not included in the workgroup's charge.

A number of guidelines, code descriptions and coding instructions, presented below, have been approved by the CPT Editorial Panel, as an affirmation of the positive direction and progress of the workgroup.

The initial set of these codes is scheduled for publication in the *CPT® 2012* code set. At that time, analytes listed in the new code set must be coded using these codes instead of the existing stacking codes (83890-83914). The current "stacking code" method of reporting molecular pathology services will be deleted upon conclusion of the workgroup's activities.

The CPT Editorial Panel understands the significance of this dramatic change in coding for large areas in molecular pathology. As an important part of the process for maintenance of the CPT code set, the MPCW is presenting the code descriptions to the public for:

- review, analysis and comparison of the code lists to determine whether other known tests:
 - are matches for these new tests
 - are not described in the listing.
- feedback from interested stakeholders.

The Editorial Panel and MPCW anticipate and welcome three potential types of feedback comments:

1. Concerns about the specific wording of any particular code descriptor.
2. Concerns that a specific analyte is not currently identified in the code list.
3. Concerns that a currently medically useful multi-analyte molecular pathology assay (MMA) is not currently identified in the code list (eg, In Vitro Diagnostic Multivariate Index Assays).

The comments and requests for revision of the code descriptors below or for additional analytes for the MPWG to consider for codification (issues 1 and 2 above) have been received and are under consideration by the MPCW. It is anticipated that by May 26th the MPCW will provide a summary of the results of consideration of these comments on this website.

Those who wish to propose codification of a multi-analyte molecular pathology assay should complete the **Molecular Pathology Code Change Application** <http://www.ama-assn.org/resources/doc/cpt/coding-change-request-form-mopath.doc> and submit this form to mopath@ama-assn.org following the submission timetable for CPT applications. As indicated in the CPT/RUC calendar <http://www.ama-assn.org/resources/doc/cpt/cpt-ruc-calendar.pdf> the next deadlines for the 2013 CPT cycle are July 13, 2011 and Nov. 2, 2011.

It is hoped that this process of review and feedback will ensure an accurate coding structure to describe non-microscopic nucleic acid analyses, to support ultimate appropriate valuation for these services, and to assist the MPCW to create future goals for identification and codification of other tests.

Workgroup Methodology

The MPCW constructed codes to describe non-infectious disease, non-microscopic, nucleic acid-based analyses to detect variations in genes that may be indicative of germline (eg, constitutional) disorders, somatic (eg, neoplasia) conditions, or histocompatibility alleles indicative of antigenic differences (eg, HLA). The nomenclature used in the codes is consistent with that described by the Human Genome Organization's (HUGO) approved gene names, as appropriate.

The MPCW acknowledges that it is not feasible to codify the entire genome in CPT and hence devised a two-tiered system. The initial set of Tier 1 codes represents, for the most part, individual analytes that are tested in sufficient volumes to warrant a specific Category I CPT code. This code list addresses the majority of commonly performed clinical molecular analyses. In contrast to the stacking codes currently used to describe genetic testing, this code list includes essentially all analytical services performed in the test (eg, cell lysis, nucleic

acid stabilization, extraction, digestion, amplification, detection and interpretation). The robust granularity of these code descriptors will furnish providers and payers with greater coding accuracy to communicate the tests that are actually performed. The unit of service for each such test is anticipated to be one (1) unless otherwise indicated.

Tier 2 codes represent medically useful procedures that are generally performed in lower volumes than Tier 1 procedures (eg, the incidence of the disease being tested is rare). They are arranged by level of technical resources and interpretive work by the physician or other qualified health care professional.

The MPCW continues to construct codes for less common analytes (surveying analyte lists such as GeneTests.org) and more complex analyses. If you wish to provide comment on the codes that have been created, please contact mopath@ama-assn.org.

It is important to note that:

- The information below is NOT final. Code assignment and final wording can be a source of confusion if portrayed as final.
- The codes and descriptors below are NOT yet available for reporting and are NOT yet recognized in any code set.
- The code numbers that precede each descriptor below are administrative alphanumeric placeholder designations used by the MPCW to track progress in construction of the code set and are not valid code numbers.
- The inclusion of an analyte in the CPT code set does not imply any health insurance coverage or reimbursement policy. While these descriptors describe a service, payment policy will determine appropriate payment for these services.

Category I Pathology and Laboratory Molecular Pathology

Molecular pathology procedures are medical laboratory procedures involving the analyses of nucleic acid to detect variants in genes that may be indicative of germline (eg, constitutional disorders) or somatic (eg, neoplasia) conditions, or to test for histocompatibility antigens (eg, HLA). Code selection is typically based on the specific gene(s) that is being analyzed. Genes are described using Human Genome Organization (HUGO) approved gene names and are italicized in the code descriptors. When the gene name is represented by an abbreviation, the abbreviation is listed first, followed by the full gene name italicized in parentheses (eg, "F5 [*coagulation Factor VJ*]"), except for the HLA series of codes. Proteins or diseases commonly associated with the genes are listed as examples in the code descriptors. The examples do not represent all conditions in which testing of the gene may be indicated.

Codes that describe tests to assess for the presence of gene variants (see definitions) use common gene variant names. Typically, all of the listed variants would be tested. However, these lists are not exclusive. If other variants are also tested in the analysis, they would be included in the procedure and not reported separately. Full gene sequencing should not be reported using codes that assess for the presence of gene variants unless specifically stated in the code descriptor.

The molecular pathology codes include all analytical services performed in the test (eg, cell lysis, nucleic acid stabilization, extraction, digestion, amplification, and detection). Any procedures required prior to cell lysis (eg, microdissection, codes 88380 and 88381) should be reported separately.

The results of the procedure may require interpretation by a physician or other qualified health care professional. When only the interpretation and report are performed, modifier 26 may be appended to the specific molecular pathology code.

All analyses are qualitative unless otherwise noted.

For microbial identification, see 87149-87153 and 87470-87801, and 87900-87904. For in situ hybridization analyses, see 88271-88275 and 88365-88368.

Molecular pathology procedures that are not specified in AXXX1-UXXX1 should be reported using the appropriate methodology codes in the 83890-83914 and 88384-88386 series.

Definitions

For purposes of reporting, the following definitions apply:

Abnormal allele: an alternative form of a gene that contains a disease-related variation from the normal sequence.

Breakpoint: the region at which a chromosome breaks during a translocation (defined elsewhere). These regions are often consistent for a given translocation.

Codon: a discrete unit of three nucleotides of a DNA or mRNA sequence that encodes a specific amino acid within, or signals the termination of, a polypeptide.

Common variants: Variants (as defined elsewhere) that are associated with compromised gene function and are interrogated in a single round of laboratory testing (in a single, typically multiplex, assay format or using more than one assay to encompass all variants to be tested). These variants typically fit the definition of a "mutation," and are usually the predominant ones causing disease. Testing for additional uncommon variants may provide additional limited value in assessment of a patient. Often there are professional society recommendations or guidelines for which variants are most appropriate to test (eg, American College of Medical Genetics/American College of Obstetrics and Gynecology guidelines for variants used in population screening for cystic fibrosis).

Constitutional: Synonymous with germline, often used in reference to the genetic code that is present at birth.

Cytogenomic: chromosome analysis using molecular techniques.

Duplication/Deletion(Dup/Del): terms that are usually used together with the '1' to refer to molecular testing, which assesses the dosage of a particular genomic region. The region tested is typically of modest to substantial size - from several dozen to several million or more nucleotides. Normal gene dosage is two copies per cell, except for the sex chromosomes (X and Y). Thus, zero or one copy represents a deletion, and three (or more) copies represent a duplication.

Dynamic mutation: Polynucleotide (eg, trinucleotide) repeats that are in or associated with genes that can undergo disease-producing increases or decreases in the numbers of repeats within tissues and across generations.

Exon: typically, one of multiple nucleic acid sequences used to encode information for a gene product (polypeptide or protein). Exons are separated from each other by non-protein-coding sequences known as introns. Exons at the respective ends of a gene also contain nucleic acid sequence that does not code for the gene's protein product.

Gene: a nucleic acid sequence that typically contains information for coding a protein as well as for the regulated expression of that protein. Human genes usually contain multiple protein coding regions (exons) separated by non-protein coding regions (introns). See also *exon*, *intron*, and *polypeptide*.

Intron: a nucleic acid sequence found between exons in human genes. An intron contains essential sequences for its proper removal (by a process known as *splicing*) to join exons together and thus facilitate production of a functional protein from a gene. An intron is sometimes referred to as an intervening sequence (IVS).

Microarray: surface(s) on which multiple specific nucleic acid sequences are attached in a known arrangement. Sometimes referred to as a 'gene chip'. Examples of uses of microarrays include evaluation of a patient specimen for gains or losses of DNA sequences (copy number variants, CNVs), identification of the presence of specific nucleotide sequence variants (also known as single nucleotide polymorphisms, SNPs), mRNA expression levels, or DNA sequence analysis.

Mutation scanning: a technique (eg, single strand conformation polymorphism, temperature gradient gel electrophoresis, etc.) typically employed on multiple PCR amplicons to indicate the presence of DNA sequence variants by differences in physical properties compared to normal. Variants are then further characterized by DNA sequence analysis only in amplicons which demonstrate differences.

Mutations: typically are variants associated with altered gene function that lead to functional deficits or disease (pathogenic).

Polymorphisms: typically are variants that do not compromise gene function or produce disease (benign).

Polypeptide: a sequence of amino acids covalently linked in a specified order. Polypeptides alone or in combination with other polypeptide subunits are the building blocks of proteins.

Short Tandem Repeat (STR): a region of DNA where a pattern of two or more nucleotides are repeated. The number of repeating segments can be used as genetic markers for human identity testing.

Single-nucleotide polymorphism (SNP): a DNA sequence variation existing at a significant frequency in the population, in which a single nucleotide (A, T, C, or G) differs between individuals and/or within an individual's paired chromosomes,

Somatic: Synonymous with acquired, referring to genetic code alterations that develop after birth (eg, occurring in neoplastic cells)

Translocation: an abnormality resulting from the breakage of a chromosome and the relocation of a portion of that chromosome's DNA sequence to the same or another chromosome. Most common translocations involve a reciprocal exchange of DNA sequences between two differently numbered (i.e., non-homologous) chromosomes, with or without a clinically significant loss of DNA.

Variant: a nucleotide sequence difference from the "normal" (predominant) sequence for a given region. Variants are typically of two types: substitutions of one nucleotide for another, and deletions or insertions of nucleotides. Occasionally, variants reflect several nucleotide sequence changes in reasonably close proximity on the same chromosomal strand of DNA (a haplotype). These nucleotide sequence variants often result in amino acid changes in the protein made by the gene. The term *variant* does not itself carry a functional implication for those protein changes.

Variants in introns are typically described in one of two ways. The altered nucleotide(s) within a defined intervening sequence (eg, IVS3-2A>G) of a gene is listed with a "+" or "-" sign, which indicates the position relative to the first or last nucleotide of the intron. Or, the variant position is indicated relative to the last nucleotide of the preceding exon or first nucleotide of the following exon (eg, c.171+1G>A c.172-1G>T are single nucleotide changes at the first and last nucleotide of a given intron for a specific gene).

The majority of the variants described here are listed by the amino acid change using the single letter amino acid code for the original amino acid followed by the numerical position in the protein product and the amino acid substitution, eg, for *ASPA* E285A, Glutamic acid (E) at position 285 is replaced with an alanine (A). A few of the variants are described by the DNA change using the numerical position followed by the original nucleotide, a greater than sign (>) and the new nucleotide, eg, *MTHFR*. 677C>T.

A known familial variant is a specific mutation that has previously been identified within a patient's family.

The following codes represent gene-specific and genomic procedures:

- AXXX1 *ASPA (aspartoacylase)* (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
- BXXX1 *BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)* (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
- BXXX2 *BCR/ABL1 (t(9;22))* (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
- BXXX3 minor breakpoint, qualitative or quantitative
- BXXX4 other breakpoint, qualitative or quantitative
- BXXX5 *BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
- BXXX6 *BRAF (v-raf murine sarcoma viral oncogene homolog B1)* (eg, colon cancer), gene analysis, V600E variant
- BXXX7 *BRCA1, BRCA2 (breast cancer 1 and 2)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common

duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

- BXXX8 185delAG, 5385insC, 6174delT variants
- BXXX9 uncommon duplication/deletion variants
- BXX10 *BRCA1 (breast cancer 1)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

(When performing BRCA1 full sequence analysis with BRCA2 full sequence analysis use BXXX7)
- BXXX11 known familial variant
- BXX12 *BRCA2 (breast cancer 2)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

(When performing BRCA2 full sequence analysis with BRCA1 full sequence analysis use BXXX7)
- BXX13 known familial variant
- CXXX1 *CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
- CXXX2 known familial variants
- CXXX3 duplication/deletion variants
- CXXX4 full gene sequence
- CXXX5 intron 8 poly-T analysis (eg, male infertility)
- CXXX6 *CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
- CXXX7 *CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- CXXX8 *CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)* (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
- CXXX9 *VKORC1 (vitamin K epoxide reductase complex, subunit 1)* (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
- CXX10 Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
- CXX11 interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

(Do not report CXX10 in conjunction with CXX11)
- FXXX1 *F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis 20210G>A variant

- FXXX2 *F5 (coagulation Factor V)* (eg, hereditary hypercoagulability) gene analysis Leiden variant
- FXXX3 *FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis common variant (eg, IVS4+4A>T)
- FXXX4 *FMR1 (Fragile X mental retardation 1)* (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

(For evaluation to detect and characterize abnormal alleles, see FXXX4, FXXX5)

(For evaluation to detect and characterize abnormal alleles using a single assay [eg, PCR], use FXXX4)
- FXXX5 characterization of alleles (eg, expanded size and methylation status)
- FXXX6 *FLT3 (fms-related tyrosine kinase 3)* (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (i.e., exons 14, 15)
- GXXX1 *G6PC (glucose-6-phosphatase, catalytic subunit)* (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis common variants (eg, R83C, Q347X)
- GXXX2 *GBA (glucosidase, beta, acid)* (eg, Gaucher disease) gene analysis common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
- HXXX1 *HEXA (hexosaminidase A (alpha polypeptide))* (eg, Tay-Sachs disease) gene analysis common variants (eg, 1278insTATC, 1421+1G>C, G269S)
- HXXX2 *HFE (hemochromatosis)* (eg, hereditary hemochromatosis) gene analysis common variants (eg, C282Y, H63D)
- HXXX3 *HBA1/HBA2 (alpha globin 1 and alpha globin 2)* (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
- IXXX1 *IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)* (eg, familial dysautonomia) gene analysis common variants (eg, 2507+6T>C, R696P)
- IXXX2 *IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplification methodology (eg, polymerase chain reaction)
- IXXX3 direct probe methodology (eg, Southern blot)
- IXXX4 *IGH@ (Immunoglobulin heavy chain locus)* (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
- IXXX5 *IGK@ (Immunoglobulin kappa light chain locus)* (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

(For immunoglobulin lambda gene [IGL@] rearrangement or immunoglobulin kappa deleting element, [IGKDEL] analysis, report the appropriate methodology code[s] in the 83890-83914 series)
- IXXX6 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] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)

- + ● IXXX7 each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
(Use IXXX7 in conjunction with IXXX6)
- IXXX8 Chimerism (engraftment) analysis, post hematopoietic stem cell transplantation specimen, includes comparison to previously performed baseline analyses; without cell selection
- IXXX9 with cell selection (eg, CD3, CD33), each cell type
(If baseline STR analysis of recipient [using buccal swab or other germline tissue sample] and donor are performed after hematopoietic stem cell transplantation, report IXXX6-IXXX7 in conjunction with IXXX8-IXXX9 for chimerism testing)
- JXXX1 *JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
- KXXX1 *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)* (eg, carcinoma) gene analysis variants in codons 12 and 13
- LXXX1 Long QT syndrome gene analyses (eg, *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2*); full sequence analysis
- LXXX2 known familial sequence variant
- LXXX3 duplication/deletion variants
- MXXX1 *MCOLN1 (mucopolipin 1)* (eg, Mucopolipidosis, type IV) gene analysis common variants (eg, IVS3-2A>G, del6.4kb)
- MXXX2 *MTHFR (5,10-methylenetetrahydrofolate reductase)* (eg, hereditary hypercoagulability) gene analysis common variants (eg, 677T, 1298C)
- MXXX3 *MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2)* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- MXXX4 known familial variants
- MXXX5 duplication/deletion variants
- MXXX6 *MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1)* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- MXXX7 known familial variants
- MXXX8 duplication/deletion variants
- MXXX9 *MSH6 (mutS homolog 6 [E. coli])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- MXXX10 known familial variants

- MXX11 duplication/deletion variants
- MXX12 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- MXX13 *MECP2 (methyl CpG binding protein 2)* (eg, Rett syndrome) gene analysis; full sequence analysis
- MXX14 known familial variant
- MXX15 duplication/deletion variants
- NXXX3 *NPM1 (nucleophosmin)* (eg, acute myeloid leukemia) gene analysis, exon 12 variants
- PXXX1 *PML/RARalpha, (t(15;17)), (PML-RARA regulated adaptor molecule 1)* (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
- PXXX2 single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative

(For intron 3 and intron 6 [including exon 6 if performed] analysis, use PXXX1)

(If both intron 6 and exon 6 are analyzed, without intron 3, use one unit of PXXX2)
- PXXX3 *PMS2 (postmeiotic segregation increased 2 [S. cerevisiae])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
- PXXX4 known familial variants
- PXXX5 duplication/deletion variants
- SXXX1 *SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal)* (eg, Niemann-Pick disease, Type A) gene analysis common variants (eg, R496L, L302P, fsP330)
- SXXX2 *SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)* (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
- SXXX3 *SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1)* (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
- TXXX1 *TCB@ (T cell antigen receptor, beta)* (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
- TXXX2 using direct probe methodology (eg, Southern blot)
- TXXX3 *TCG@ (T cell antigen receptor, gamma)* (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

(For T cell antigen alpha [*TCA@*] gene rearrangement analysis, report the appropriate methodology code(s) in the 83890-83914 series)

(For T cell antigen delta [TCD@] gene rearrangement analysis, report L2XX2)

- UXXX1 *UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1)* (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)

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 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 (eg, HLA-B*27 and ankylosing spondylitis and HLA-B*57:01 and abacavir hypersensitivity) as well as other clinical uses. One or more HLA genes may be tested in specific clinical situations (eg, HLA-DQB1 for narcolepsy and HLA-A, -B, -C, -DRB1 and -DQB1 for kidney transplantation). Each HLA gene typically has multiple variant alleles or alleles groups that can be identified by typing. For HLA result reporting, a low resolution HLA type is denoted by a two digit HLA name (eg, A*02) and high resolution typing is denoted by a greater number of digits (eg, A*02:02, *03:01:01:01, and C*03:04P). If additional testing is required to resolve ambiguous allele combinations for high resolution typing, it is included in the HLA typing code. The gene names have been italicized similar to the other molecular pathology codes.

(For HLA antigen typing by non-molecular pathology techniques, see 86812-86822)

- HLXX1 HLA Class I and II typing, low resolution (eg, antigen equivalents); *HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1*
- HLXX2 *HLA-A, -B, and -DRB1/3/4/5* (eg, verification typing)
- HLXX3 HLA Class I typing, low resolution (eg, antigen equivalents); complete (i.e., *HLA-A, -B, and -C*)
(When performing both Class I and II low resolution HLA typing for *HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1*, use HLXX1)
- HLXX4 one locus (eg, *HLA-A, -B, or -C*), each
(When performing a complete Class I [*HLA-A, -B, and -C*] low resolution HLA typing, use HLXX3)
(When the presence or absence of a single antigen equivalent is reported using low resolution testing, use HLXX5)
- HLXX5 one antigen equivalent (eg, *B*27*), each
(When testing for presence or absence of more than 2 antigen equivalents at a locus, use HLXX4 for each locus tested)
- HLXX6 HLA Class II typing, low resolution (eg, antigen equivalents); *HLA-DRB1/3/4/5 and -DQB1*
(When performing both Class I and II low resolution HLA typing for *HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1*, use HLXX1)
- HLXX7 one locus (eg, *HLA-DRB1/3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1*), each
(When low resolution typing is performed for *HLA-DRB1/3/4/5 and -DQB1*, use HLXX6)
(For low resolution typing, *HLA-DRB1/3/4/5* should be treated as a single locus)

- HLXX8 one antigen equivalent, each
(When testing for presence or absence of more than 2 antigen equivalents at a locus, use HLXX7 for each locus)
- HLXX9 HLA Class I and II typing, high resolution (i.e., alleles or allele groups), *HLA-A, -B, -C, and -DRB1*
- HLX10 HLA Class I typing, high resolution (i.e., alleles or allele groups); complete (i.e., *HLA-A, -B, and -C*)
- HLX11 one locus (eg, *HLA-A, -B, or -C*), each
(When a complete Class I high resolution typing for *HLA-A, -B, and -C* is performed, use HLX10)
(When the presence or absence of a single allele or allele group is reported using high resolution testing, use HLX12)
- HLX12 one allele or allele group (eg, *B*57:01P*), each
(When testing for the presence or absence of more than 2 alleles or allele groups at a locus, use HLX11 for each locus)
- HLX13 HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (eg, *HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1*), each
(When only the presence or absence of a single allele or allele group is reported using high resolution testing, use HLX14)
- HLX14 one allele or allele group (eg, *HLA-DQB1*06:02P*), each
(When testing for the presence or absence of more than 2 alleles or allele groups at a locus, use HLX13 for each locus)

Tier 2 Molecular Pathology Procedures

The following Molecular Pathology Procedure (Tier 2) codes are used to report procedures not listed in the Tier 1 molecular pathology codes (AXXX1-UXXX1). They represent medically useful procedures that are generally performed in lower volumes than Tier 1 procedures (eg, the incidence of the disease being tested is rare). They are arranged by level of technical resources and interpretive work by the physician or other qualified health care professional. The individual analyses listed under each code (i.e., level of procedure) utilize the definitions and coding principles as described in the introduction preceding the Tier 1 molecular pathology codes. The parenthetical examples of methodologies presented near the beginning of each code provide general guidelines used to group procedures for a given level and are not all-inclusive.

Use the appropriate molecular pathology procedure level code that includes the specific analyte listed after the code descriptor. If the analyte tested is not listed under one of the Tier 2 codes or is not represented by a Tier 1 code, use the appropriate methodology codes in the 83890-83914 and 88384-88386 series.

- L2XX1 Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD) (eg, medium chain acyl dehydrogenase deficiency), K304E variant

ACE (angiotensin converting enzyme) (eg, hereditary blood pressure regulation), insertion/deletion variant

AGTR1 (angiotensin II receptor, type 1) (eg, essential hypertension), 1166A>C variant

CCR5 (chemokine C-C motif receptor 5) (eg, HIV resistance), 32-bp deletion mutation/794 825del32 deletion

DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), IVS14+1G>A variant

F2 (coagulation factor 2) (eg, hereditary hypercoagulability), 1199G>A variant

F5 (coagulation factor V) (eg, hereditary hypercoagulability), HR2 variant

F7 (coagulation factor VII [serum prothrombin conversion accelerator]) (eg, hereditary hypercoagulability), R353Q variant

FGB (fibrinogen beta chain) (eg, hereditary ischemic heart disease), -455G>A variant

F13B (coagulation factor XIII, B polypeptide) (eg, hereditary hypercoagulability), V34L variant

SERPINE1 (serpine peptidase inhibitor clade E, member 1, plasminogen activator inhibitor -1, PAI-1) (eg, thrombophilia), 4G variant

● L2XX2

Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

ABL (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib resistance), T315I variant

ACADM (acyl-CoA dehydrogenase, C-4 to C-12 straight chain, MCAD) (eg, medium chain acyl dehydrogenase deficiency), common variants (eg, K304E, Y42H)

ADRB2 (adrenergic beta-2 receptor surface) (eg, drug metabolism), common variants (eg, G16R, Q27E)

APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)

CBFB/MYH11 (inv(16)) (eg, acute myeloid leukemia), qualitative, and quantitative, if performed

CCND1/IgH (BCL1/IgH, t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative, and quantitative if performed

CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6)

CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6)

CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2])

DMPK (dystrophia myotonica-protein kinase) (eg, myotonic dystrophy, type 1), evaluation to detect abnormal (eg, expanded) alleles

F11 (coagulation factor XI) (eg, coagulation disorder), common variants (eg, E117X [Type II], F283L [Type III], IVS14del14, and IVS14+1G>A [Type I])

FGFR3 (fibroblast growth factor receptor 3) (eg, achondroplasia), common variants (eg, 1138G>A, 1138G>C)

FIP1L1/PDGFR4 (del[4q12]) (eg, imatinib-sensitive chronic eosinophilic leukemia), qualitative, and quantitative, if performed

GALT (galactose-1-phosphate uridylyltransferase) (eg, galactosemia), common variants (eg, Q188R, S135L, K285N, T138M, L195P, Y209C, IVS2-2A>G, P171S, del5kb, N314D, L218L/N314D)

HBB (hemoglobin, beta) (eg, sickle cell anemia, hemoglobin C, hemoglobin E), common variants (eg, HbS, HbC, HbE)

HTT (huntingtin) (eg, Huntington disease), evaluation to detect abnormal (eg, expanded) alleles

RUNX1/RUNX1T1 (t[8;21]) (eg, acute myeloid leukemia) translocation analysis, qualitative, and quantitative, if performed

TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), common variants (eg, *2, *3)

VWF (von Willebrand factor) (eg, von Willebrand disease type 2N), common variants (eg, T791M, R816W, R854Q)

● L2XX3

Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon)

CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (eg, congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (eg, IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30-kb deletion variant)

KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), common variants (eg, D816V, D816Y, D816F)

MEFV (Mediterranean fever) (eg, familial Mediterranean fever), common variants (eg, E148Q, P369S, F479L, M680I, I692del, M694V, M694I, K695R, V726A, A744S, R761H)

TCD@ (T cell antigen receptor, delta) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population

● L2XX4

Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

ABL1 (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), variants in the kinase domain

DAZ/SRY (deleted in azoospermia and sex determining region Y) (eg, male infertility), common deletions (eg, AZFa, AZFb, AZFc, AZFd)

JAK2 (*Janus kinase 2*) (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed

MPL (*myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR*) (eg, myeloproliferative disorder), exon 10 sequence

VHL (*von Hippel-Lindau tumor suppressor*) (eg, von Hippel-Lindau familial cancer syndrome), deletion/duplication analysis

VWF (*von Willebrand factor*) (eg, von Willebrand disease types 2A, 2B, 2M), targeted sequence analysis (eg, exon 28)

● L2XX5

Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

BTD (*biotinidase*) (eg, biotinidase deficiency), full gene sequence

CYP1B1 (*cytochrome P450, family 1, subfamily B, polypeptide 1*) (eg, primary congenital glaucoma), full gene sequence

DMPK (*dystrophia myotonica-protein kinase*) (eg, myotonic dystrophy type 1), characterization of abnormal (eg, expanded) alleles

FKRP (*Fukutin related protein*) (eg, congenital muscular dystrophy type 1C [MDC1C], limb-girdle muscular dystrophy [LGMD] type 2I), full gene sequence

FOXG1 (*forkhead box G1*) (eg, Rett syndrome), full gene sequence

FSHMD1A (*facioscapulohumeral muscular dystrophy 1A*) (eg, facioscapulohumeral muscular dystrophy), evaluation to detect abnormal (eg, deleted) alleles

HBB (*hemoglobin, beta, Beta-Globin*) (eg, thalassemia), full gene sequence

KIT (*C-kit*) (*v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog*) (eg, GIST, acute myeloid leukemia, melanoma), targeted gene analysis (eg, exons 8, 11, 13, 17, 18)

MEFV (*Mediterranean fever*) (eg, familial Mediterranean fever), full gene sequence

NRAS (*neuroblastoma RAS viral oncogene homolog*) (eg, colorectal carcinoma), exon 1 and exon 2 sequences

PDGFRA (*platelet-derived growth factor receptor alpha polypeptide*) (eg, gastrointestinal stromal tumor), targeted sequence analysis (eg, exons 12, 18)

RET (*ret proto-oncogene*) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)

SDHD (*succinate dehydrogenase complex, subunit D, integral membrane protein*) (eg, hereditary paraganglioma), full gene sequence

VHL (*von Hippel-Lindau tumor suppressor*) (eg, von Hippel-Lindau familial cancer syndrome), full gene sequence

VWF (*von Willebrand factor*) (eg, von Willebrand disease type 1C), targeted sequence analysis (eg, exons 26, 27, 37)

- L2XX6 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
 - CYP21A2* (*cytochrome P450, family 21, subfamily A, polypeptide2*) (eg, steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence
 - FKTN* (*Fukutin*) (eg, limb-girdle muscular dystrophy [LGMD] type 2M or 2L), full gene sequence
 - RET* (*ret proto-oncogene*) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)
 - SDHB* (*succinate dehydrogenase complex, subunit B, iron sulfur*) (eg, hereditary paraganglioma), full gene sequence
 - TGFBR1* (*transforming growth factor, beta receptor 1*) (eg, Marfan syndrome), full gene sequence
 - TGFBR2* (*transforming growth factor, beta receptor 2*) (eg, Marfan syndrome), full gene sequence
 - THRB* (*thyroid hormone receptor, beta*) (eg, thyroid hormone resistance, thyroid hormone beta receptor deficiency), full gene sequence or targeted sequence analysis of >5 exons
 - TP53* (*tumor protein 53*) (eg, Li-Fraumeni syndrome, tumor samples), full gene sequence or targeted sequence analysis of >5 exons
 - VWF* (*von Willebrand factor*) (eg, von Willebrand disease type 2N), targeted sequence analysis (eg, exons 18-20, 23-25)
- L2XX7 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
 - CAPN3* (*Calpain 3*) (eg, limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence
 - GALT* (*galactose-1-phosphate uridylyltransferase*) (eg, galactosemia), full gene sequence
 - HEXA* (*hexosaminidase A, alpha polypeptide*) (eg, Tay-Sachs disease), full gene sequence
 - LMNA* (*lamin A/C*) (eg, Emery-Dreifuss muscular dystrophy [EDMD1, 2 and 3] limb-girdle muscular dystrophy [LGMD] type 1B, dilated cardiomyopathy [CMD1A], familial partial lipodystrophy [FPLD2]), full gene sequence
 - PAH* (*phenylalanine hydroxylase*) (eg phenylketonuria), full gene sequence
 - POMGNT1* (*protein O-linked mannose beta1,2-N acetylglucosaminyltransferase*) (eg, Muscle-Eye-Brain disease, Walker-Warburg syndrome), full gene sequence
 - POMT1* (*protein-O-mannosyltransferase 1*) (eg, limb-girdle muscular dystrophy [LGMD] type 2K, Walker-Warburg syndrome), full gene sequence

POMT2 (protein-O-mannosyltransferase 2) (eg, limb-girdle muscular dystrophy [LGMD] type 2N, Walker-Warburg syndrome), full gene sequence

RYR1 (ryanodine receptor 1, skeletal) (eg, malignant hyperthermia), targeted sequence analysis of exons with functionally-confirmed mutations

VWF (von Willebrand factor) (von Willebrand disease type 2A), extended targeted sequence analysis (eg, exons 11-16, 24-26, 51, 52)

- L2XX8 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)

SCN1A (sodium channel, voltage-gated, type 1, alpha subunit) (eg, generalized epilepsy with febrile seizures), full gene sequence

- L2XX9 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)

FBN1 (fibrillin 1) (eg, Marfan syndrome), full gene sequence

NF1 (neurofibromin 1) (eg, neurofibromatosis, type 1), full gene sequence

RYR1 (ryanodine receptor 1, skeletal) (eg, malignant hyperthermia), full gene sequence

VWF (von Willebrand factor) (eg, von Willebrand disease types 1 and 3), full gene sequence