CMS Manual System	**Department of Health & Human Services (DHHS)**
Pub 100-04 Medicare Claims Processing	**Centers for Medicare & Medicaid Services (CMS)**
Transmittal 13102	**Date: March 13, 2025**
	Change Request 13959

SUBJECT: Healthcare Common Procedure Coding System (HCPCS) Codes Subject to and Excluded from Clinical Laboratory Improvement Amendments (CLIA) Edits

I. SUMMARY OF CHANGES: The purpose of this Change Request (CR) is to inform contractors about the new HCPCS codes for 2025 that are subject to and excluded from CLIA edits. This Recurring Update Notification (RUN) applies to Chapter 16, section 70.9.

EFFECTIVE DATE: April 1, 2025
**Unless otherwise specified, the effective date is the date of service.*
IMPLEMENTATION DATE: April 7, 2025

Disclaimer for manual changes only: The revision date and transmittal number apply only to red italicized material. Any other material was previously published and remains unchanged. However, if this revision contains a table of contents, you will receive the new/revised information only, and not the entire table of contents.

II. CHANGES IN MANUAL INSTRUCTIONS: (N/A if manual is not updated)
R=REVISED, N=NEW, D=DELETED-*Only One Per Row.*

R/N/D	CHAPTER / SECTION / SUBSECTION / TITLE
N/A	N/A

III. FUNDING:

For Medicare Administrative Contractors (MACs):
The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the Contracting Officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the Contracting Officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

IV. ATTACHMENTS:

Recurring Update Notification

Attachment - Recurring Update Notification

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II. GENERAL INFORMATION

A. Background: The Clinical Laboratory Improvement Amendments (CLIA) regulations require a facility to be appropriately certified for each test performed. To ensure that Medicare & Medicaid only pay for laboratory tests performed in certified facilities, each claim for a HCPCS code that is considered a CLIA laboratory test is currently edited at the CLIA certificate level.

The HCPCS codes that are considered a laboratory test under CLIA change each year. Contractors need to be informed about the new HCPCS codes that are both subject to CLIA edits and excluded from CLIA edits.

The following HCPCS codes were discontinued on October 1, 2024:

- 0167U Gonadotropin, chorionic (hCG), immunoassay with direct optical observation, blood; and
- 0396U Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions.

The following HCPCS codes were discontinued on January 1, 2025:

- 0346U Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC- MS/MS), ratio, plasma;
- 0352U Detection of bacteria causing vaginosis and vaginitis by multiplex amplified;
- 0380U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype;
- 0428U Oncology (breast), targeted hybridcapture genomic sequence analysis panel, circulating tumor DNA (ctDNA) analysis of 56 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutation burden;
- 0448U Oncology (lung and colon cancer), DNA, qualitative, next- generation sequencing detection; and
- 0456U Autoimmune (rheumatoid arthritis), next generation sequencing (NGS), gene expression testing of 19 genes, whole blood, with analysis of anti- cyclic citrullinated peptides (CCP) levels, combined with sex, patient global assessment, and body mass index (BMI), algorithm reported as a score that predicts.

The HCPCS codes that follow are all subject to CLIA edits. These lists do not include new HCPCS codes for waived tests or provider-performed microscopy procedures. All of these HCPCS codes require a facility

to have either a CLIA certificate of registration (certificate type code 9), a CLIA certificate of compliance (certificate type code 1), or a CLIA certificate of accreditation (certificate type code 3). A facility without a valid, current, CLIA certificate, with a current CLIA certificate of waiver (certificate type code 2) or with a current CLIA certificate for provider-performed microscopy procedures (certificate type code 4) must not be permitted to be paid for these tests, unless a facility with a current CLIA certificate of waiver (certificate type code 2) or CLIA certificate for provider-performed microscopy procedures (certificate type code 4) bills the appropriate HCPCS service code with a QW modifier.

The HCPCs code listed below was added on July 1, 2024, and is subject to CLIA edits.

0020M Oncology (central nervous system), analysis of 30000 DNA methylation loci by methylation array, utilizing DNA extracted from tumor tissue, diagnostic algorithm reported as probability of matching a reference tumor subclass.

The HCPCS codes listed below were added on October 1, 2024, and are subject to CLIA edits.

0476U Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes;

0477U Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes;

0478U Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection;

0479U Tau, phosphorylated, pTau217;

0480U Infectious disease (bacteria, viruses, fungi, and parasites), cerebrospinal fluid (CSF), metagenomic next-generation sequencing (DNA and RNA), bioinformatic analysis, with positive pathogen identification;

0481U IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (eg, central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions);

0482U Obstetrics (preeclampsia), biochemical assay of soluble fmslike tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), serum, ratio reported for sFlt1/PlGF, with risk of progression for preeclampsia with severe features within 2 weeks;

0483U Infectious disease (Neisseria gonorrhoeae), sensitivity, ciprofloxacin resistance (gyrA S91F point mutation), oral, rectal, or vaginal swab, algorithm reported as probability of fluoroquinolone resistance;

0484U Infectious disease (Mycoplasma genitalium), macrolide sensitivity (23S rRNA point mutation), oral, rectal, or vaginal swab, algorithm reported as probability of macrolide resistance;

0485U Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden;

0486U Oncology (pan-solid tumor), nextgeneration sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction;

0487U Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidycorrected gene copy number amplifications and losses, gene rearrangements, and microsatellite instability;

0488U Obstetrics (fetal antigen noninvasive prenatal test), cellfree DNA sequence analysis for detection of fetal presence or absence of 1 or more of the Rh, C, c, D, E, Duffy (Fya), or Kell (K) antigen in alloimmunized pregnancies, reported as selected antigen(s) detected or not detected;

0489U Obstetrics (single-gene noninvasive prenatal test), cellfree DNA sequence analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants, and relative mutation-dosage analysis based on molecular counts to determine fetal inheritance of maternal mutation, algorithm reported as a fetal risk score for the condition (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia);

0490U Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanomaassociated antigen, CD34 and CD45 protein biomarkers, peripheral blood;

0491U Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood;

0492U Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarkerexpressing cells, peripheral blood;

0493U Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using nextgeneration sequencing, plasma, reported as percentage of donorderived cell-free DNA;

0494U Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative;

0495U Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer;

0496U Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk;

0497U Oncology (prostate), mRNA geneexpression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalinfixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer;

0498U Oncology (colorectal), nextgeneration sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation;

0499U Oncology (colorectal and lung), DNA from formalin-fixed paraffinembedded (FFPE) tissue, nextgeneration sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection;

0500U Autoinflammatory disease (VEXAS syndrome), DNA, UBA1 gene mutations, targeted variant analysis (M41T, M41V, M41L, c.118-2A>C, c.118-1G>C, c.1189_118-2del, S56F, S621C);

0501U Oncology (colorectal), blood, quantitative measurement of cellfree DNA (cfDNA);

0502U Human papillomavirus (HPV), E6/E7 markers for high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), cervical cells, branched-chain capture hybridization, reported as negative or positive for high risk for HPV;

0503U Neurology (Alzheimer disease), beta amyloid (Aβ40, Aβ42, Aβ42/40 ratio) and tau-protein (ptau217, np-tau217, ptau217/nptau217 ratio), blood, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS), algorithm score reported as likelihood of positive or negative for amyloid plaques;

0504U Infectious disease (urinary tract infection), identification of 17 pathologic organisms, urine, realtime PCR, reported as positive or negative for each organism;

0505U Infectious disease (vaginal infection), identification of 32 pathogenic organisms, swab, real-time PCR, reported as positive or negative for each organism;

0506U Gastroenterology (Barrett's esophagus), esophageal cells, DNA methylation analysis by next-generation sequencing of at least 89 differentially methylated genomic regions, algorithm reported as likelihood for Barrett's esophagus;

0507U Oncology (ovarian), DNA, wholegenome sequencing with 5hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected;

0508U Transplantation medicine, quantification of donor-derived cell-free DNA using 40 singlenucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cellfree 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;

0510U Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA wholetranscriptome data, reported as probability of predicted molecular subtype;

0511U Oncology (solid tumor), tumor cell culture in 3D microenvironment, 36 or more drug panel, reported as tumor-response prediction for each drug;

0512U Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffinembedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H);

0513U Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalinfixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker;

0514U Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of adalimumab (ADL) levels in venous serum in patients undergoing adalimumab therapy, results reported as a numerical value as micrograms per milliliter (µg/mL);

0515U Gastroenterology (irritable bowel disease [IBD]), immunoassay for quantitative determination of infliximab (IFX) levels in venous serum in patients undergoing infliximab therapy, results reported as a numerical value as micrograms per milliliter (µg/mL);

0516U Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status;

0517U Therapeutic drug monitoring, 80 or more psychoactive drugs or substances, LC-MS/MS, plasma, qualitative and quantitative therapeutic minimally and maximally effective dose of prescribed and non-prescribed medications;

0518U Therapeutic drug monitoring, 90 or more pain and mental health drugs or substances, LC-MS/MS, plasma, qualitative and quantitative therapeutic minimally effective range of prescribed and non-prescribed medications;

0519U Therapeutic drug monitoring, medications specific to pain, depression, and anxiety, LCMS/MS, plasma, 110 or more drugs or substances, qualitative and quantitative therapeutic minimally effective range of prescribed, non-prescribed, and illicit medications in circulation;

0520U Therapeutic drug monitoring, 200 or more drugs or substances, LCMS/MS, plasma, qualitative and quantitative therapeutic minimally effective range of prescribed and non-prescribed medications.

The HCPCS codes listed below were added on January 1, 2025, are subject to CLIA edits.

81195 Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (ogm)

81515 Infectious disease, bacterial vaginosis and vaginitis, real-time pcr amplification of dna markers for atopobium vaginae, atopobium species, megasphaera type 1, and bacterial vaginosis associated bacteria-2 (bvab-2), utilizing vaginal-fluid specimens, algorithm reported as positive or negative for high likelihood of bacterial vaginosis, includes separate detection of trichomonas vaginalis and candida species (c. albicans, c. tropicalis, c. parapsilosis, c. dubliniensis), candida glabrata/candida krusei, when reported

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

82233 Beta-amyloid; 1-40 (abeta 40)

82234 Beta-amyloid; 1-42 (abeta 42)

83884 Neurofilament light chain (nfl)

84393 Tau, phosphorylated (eg, ptau 181, ptau 217), each

84394 Tau, total (ttau)

86581 Streptococcus pneumoniae antibody (igg), serotypes, multiplex immunoassay, quantitative

87513 Infectious agent detection by nucleic acid (dna or rna); helicobacter pylori (h. pylori), clarithromycin resistance, amplified probe technique

87564 Infectious agent detection by nucleic acid (dna or rna); mycobacterium tuberculosis, rifampin resistance, amplified probe technique

87594 Infectious agent detection by nucleic acid (dna or rna); pneumocystis jirovecii, amplified probe technique

87626 Infectious agent detection by nucleic acid (dna or rna); human papillomavirus (hpv), separately reported high-risk types (eg, 16, 18, 31, 45, 51, 52) and high-risk pooled result(s)

0521U Rheumatoid factor IgA and IgM, cyclic citrullinated peptide (CCP) antibodies, and scavenger receptor A (SR-A) by immunoassay, blood;

0522U Carbonic anhydrase VI, parotid specific/secretory protein and salivary protein 1 (SP1), IgG, IgM, and IgA antibodies, chemiluminescence, semiqualitative, blood;

0523U Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single- nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin- embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change;

0524U Obstetrics (preeclampsia), sFlt- 1/PlGF ratio, immunoassay, utilizing serum or plasma, reported as a value;

0525U Oncology, spheroid cell culture, 11-drug panel (carboplatin, docetaxel, doxorubicin, etoposide, gemcitabine, niraparib, olaparib, paclitaxel, rucaparib, topotecan, veliparib) ovarian, fallopian, or peritoneal response prediction for each drug;

0526U Nephrology (renal transplant), quantification of CXCL10 chemokines, flow cytometry, urine, reported as pg/mL creatinine baseline and monitoring over time;

0527U Herpes simplex virus (HSV) types 1 and 2 and Varicella zoster virus (VZV), amplified probe technique, each pathogen reported as detected or not detected;

0528U Lower respiratory tract infectious agent detection, 18 bacteria, 8 viruses, and 7 antimicrobial-resistance genes, amplified probe technique, including reverse transcription for RNA targets, each analyte reported as detected or not detected with semiquantitative results for 15 bacteria";

0529U Hematology (venous thromboembolism [VTE]), genome-wide single-nucleotide polymorphism variants, including F2 and F5 gene analysis, and Leiden variant, by microarray analysis, saliva, report as risk score for VTE; and

0530U Oncology (pan-solid tumor), ctDNA, utilizing plasma, next- generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy-number alterations, with therapy association.

"***NOTE*** This instruction is NOT intended to rescind/replace any previous instructions indicating that a laboratory with a valid CLIA certificate of waiver or CLIA certificate for provider-performed microscopy procedures be allowed to bill the above codes with a QW modifier.

This RUN applies to Chapter 16, Section 70.9.

B. Policy: The CLIA regulations require a facility to be appropriately certified for each test performed. To ensure that Medicare and Medicaid only pay for laboratory tests in a facility with a valid, current CLIA certificate, laboratory claims are currently edited at the CLIA certificate level.

III. BUSINESS REQUIREMENTS TABLE

"Shall" denotes a mandatory requirement, and "should" denotes an optional requirement.

Number	Requirement	Responsibility								
		A/B MAC			DME	Shared-System Maintainers				Other
		A	B	HHH	MAC	FISS	MCS	VMS	CWF	
13959.1	Contractors shall apply CLIA edits to the HCPCS codes mentioned above as subject to CLIA edits.		X						X	
13959.1.1	Contractors shall add the following codes to CWF Category 69 to avoid inappropriate setting of the CWF Edit 8617. 86769 - Quidel Sofia 2, Effective September 20, 2023 81514 - Cepheid GeneXpert Xpress System {Xpert Xpress MVP}, Effective October 19, 2023								X	
13959.2	Contractors shall deny payment for a claim submitted with the HCPCS codes mentioned above as subject to CLIA edits to a provider without valid current CLIA certificate, with a CLIA certificate of waiver (certificate type code 2) (when billed ***without*** the 'QW' modifier), or with a CLIA certificate for provider-performed microscopy procedures (certificate type code 4) (when billed ***without*** the 'QW' modifier).		X							
13959.3	Contractors shall return a claim as unprocessable if a CLIA number is not submitted on claims by providers for the HCPCS mentioned above as subject to CLIA edits.		X							
13959.4	Contractors shall not search their files to either retract		X							

Number	Requirement	Responsibility								
		A/B MAC			DME	Shared-System Maintainers				Other
		A	B	HHH	MAC	FISS	MCS	VMS	CWF	
	payment for claims already paid or to retroactively pay claims. However, contractors shall adjust claims brought to their attention.									

IV. PROVIDER EDUCATION

Medicare Learning Network® (MLN): CMS will develop and release national provider education content and market it through the MLN Connects® newsletter shortly after we issue the CR. MACs shall link to relevant information on your website and follow IOM Pub. No. 100-09 Chapter 6, Section 50.2.4.1 for distributing the newsletter to providers. When you follow this manual section, you don't need to separately track and report MLN content releases. You may supplement with your local educational content after we release the newsletter.

Impacted Contractors: A/B MAC Part B

V. SUPPORTING INFORMATION

Section A: Recommendations and supporting information associated with listed requirements:

"Should" denotes a recommendation.

X-Ref Requirement Number	Recommendations or other supporting information:
	N/A

Section B: All other recommendations and supporting information: N/A

VI. CONTACTS

Post-Implementation Contact(s): Contact your Contracting Officer's Representative (COR).

VII. FUNDING

Section A: For Medicare Administrative Contractors (MACs):
The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the Contracting Officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the Contracting Officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

ATTACHMENTS: 0