ASSOCIATION FOR MOLECULAR PATHOLOGY

Providing global expertise in molecular testing that drives patient care

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October 27, 2023

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Submitted electronically via CLFS_Annual_Public_Meeting@cms.hhs.gov

RE: Preliminary Determinations for Calendar Year 2024 (CY2024) for New and Reconsidered Services on the Clinical Laboratory Fee Schedule (CLFS)

Dear Administrator Brooks-LaSure:

On behalf of the Association for Molecular Pathology (AMP), thank you for the opportunity to submit comments on preliminary determinations on the Clinical Laboratory Fee Schedule (CLFS) for calendar year 2024 (CY2024) for new and reconsidered codes. AMP is an international medical and professional association representing approximately 2,900 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Our membership includes professionals from the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics (IVD) industry. AMP members are experts in molecular pathology, and the implementation, coverage, and payment determinations for the codes on the CLFS directly impact their practice. Therefore, we share CMS' goal to appropriately price each code on the CLFS to protect Medicare beneficiary access to testing.

AMP presented recommendations at the CLFS Annual Public Meeting on June 22, 2023. In this letter, we share our concerns about the Clinical Laboratory Fee Schedule (CLFS) Calendar Year 2024 (CY2024) preliminary determinations, which we fear may lead to suboptimal prices that do not adequately account for the work and resources required to perform each test and, if prices are not adjusted, may limit beneficiary access to these necessary services. Specifically, AMP disagrees with the preliminary determinations for genomic sequencing procedures (GSP) CPT codes 8X017, 8X018, 8X019, 8X020, 8X021, and 8X022 (Table 1). These CPT codes were developed by the AMA CPT Tumor Genomics workgroup to address identification and reporting of additional biomarkers such as Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI).

Table 1: Comparison of AMP Recommendations and CMS CY2024 CLFS Preliminary Determinations

CPT Code	AMP Recommendation	CMS CY2024 CLFS Preliminary Determination
8X017 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability	*Crosswalk to CPT **81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis Minus CPT 81277 as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. 8X017 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.
8X018 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability	*Crosswalk to CPT **81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. 8X018 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.
8X019 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	*Crosswalk to CPT **0244U** Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. 8X019 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.
8X020 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements	*Crosswalk to CPT **81455 (x 1.25)** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. The descriptor for 8X020 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.

8X021 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability	*Crosswalk to CPT **81455 (x 1.25)** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. The descriptor for 8X021 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.
8X022 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	Crosswalk to CPT **0244U (x 1.25)** Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue as comparable resources are used.	Crosswalk to 81445. CMS disagrees with the majority of the CDLT Panel and instead is recommending a different crosswalk. The descriptor for 8X022 does not specify what is being analyzed, therefore CMS does not see justification in crosswalking to a code that specifies analyzing more than 50 genes. CMS is instead proposing a crosswalk that analyzes 5-50 genes.

* The Clinical Diagnosis Laboratory Tests (CDLT) panel unanimously voted for this crosswalk (9 out of 9 votes)

AMP is concerned with CMS' preliminary decision to crosswalk all new CPT codes 8X017, 8X018, 8X019, 8X020, 8X021, and 8X022 to CPT code 81445 (Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 gene) which was not congruent with the recommendations of the Clinical Diagnostic Laboratory Test (CDLT) Advisory Panel (see Table 1). The crosswalk for these services should not be solely based on gene number, as mentioned in the preliminary determinations and The new CPT codes 8X017-8X022 are comprehensive genomic profile (CGP) testing, defined by MolDx as a Next Generations Sequencing (NGS)-based molecular assays that provide additional insight beyond individual gene hotspots and which seek to describe the genomic makeup of a tumor and can help identify underlying mechanisms of disease to guide clinical decision-making.[1] Of note, CGP is not defined as a targeted panel by MolDX and therefore cannot be analyzed as a targeted panel such as 81445.

Instead, it is essential to define the work performed by clinical laboratories comprehensively, considering the diverse types of variants as a surrogate to identify the breadth of work (see Table 2). Sequencing has evolved to a point where the incremental number of genes on a panel does not systematically translate into a significantly higher level of resources, but the types of variants and attributes detected have a clear impact on validation work required, sequencing reagents needed, size and capacity of instrumentation, and bioinformatic resources to run multiple algorithms for accurate reporting. Furthermore, these new codes account for such work Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI), which were previously unaccounted for in CPT coding and require more

[1] https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=55197

work and resources to complete in comparison to a targeted panel. For these reasons, AMP asks CMS to reconsider its approach to crosswalk determinations by acknowledging the importance of considering different types of variants and aligning with established guidelines for comprehensive testing.

Table 2: Comparison of oncology GSP CPT codes (from CPT 2024)

Code	Specimen Source			Nucleic Acid	Sequence Variants	Copy Number Variants	Microsatellite Instability	Tumor Mutation Burden	Rearrangements
	Solid Organ	Hematolymphoid	Cell-Free						
81445	X		No	DNA or DNA/RNA	X	X			X
81449	X		No	RNA	X				X
81450		X	No	DNA or DNA/RNA	X	X			X
81451		X	No	RNA	X				X
81455	X	X	No	DNA or DNA/RNA	X	X			X
81456	X	X	No	RNA	X				X
81457 (8X017)	X		No	DNA	X		X		
81458 (8X018)	X		No	DNA	X	X	X		
81459 (8X019)	X		No	DNA or DNA/RNA	X	X	X	X	X
81462 (8X020)	X		Yes	DNA or DNA/RNA	X	X			X
81463 (8X021)	X		Yes	DNA	X	X	X		
81464 (8X022)	X		Yes	DNA or DNA/RNA	X	X	X	X	X

Formalin-Fixed Paraffin-Embedded Tissue and Cell-Free Nucleic Acid Testing

The abovementioned GSP codes have two different sample types used in the testing, Formalin-Fixed Paraffin-Embedded (FFPE) Tissue and Cell-Free Nucleic Acid Testing. The work and resources needed differ between the sample types in an assay using Cell-Free Nucleic Acid Testing is more labor intensive and more expensive than FFPE. Kits that isolate cell free DNA (cfDNA) for analysis cost more than kits to isolate DNA from Formalin-Fixed Paraffin-Embedded Tissue[2,3]. Furthermore, the work and expertise of a molecular pathologist to interpret results is higher for Cell-Free Nucleic Acid Testing as the depth of sequencing is an order of magnitude higher than FFPE tissue, i.e. cfDNA requires 10,000x depth of sequencing versus FFPE Tissue with 100-1,000x. For these reasons, AMP is seeking a 1.25 multiplier for codes using Cell-Free Nucleic Acid Testing as we believe it adequately reflects the work and resources used when going from FFPE Tissue to Cell-Free Nucleic Acid Testing.

[2] https://www.qiagen.com/us/products/discovery-and-translational-research/dna-rna-purification/dna-purification/cell-free-dna/qiaamp-circulating-nucleic-acid-kit

[3] https://www.qiagen.com/us/products/discovery-and-translational-research/dna-rna-purification/dna-purification/genomic-dna/qiaamp-dna-ffpe-tissue-kit

Tumor Mutational Burden and Microsatellite Instability

Both TMB and MSI are predictive biomarkers that can provide more precise and comprehensive data for determining the potential efficacy of immunotherapies for cancer[4]. This testing can help determine patient treatments and has been shown to improve patient outcomes[5].

Tumor Mutational Burden (TMB) is a complex biomarker analysis that requires significant bioinformatics and development/validation requirements, and therefore requires additional work and resources beyond test code CPT code 81455. Due to the amount of DNA required to analyze TMB (300 or more genes), it is measured in mega-bases rather than the number of genes. TMB is defined in the 2024 CPT code book in the Preface of the GSP section as "the number of somatic mutations detected per million bases, or Megabase (Mb) of genomic sequence investigated from a cancer specimen. It is usually obtained from analysis using a next generation sequencing method. It is considered a biomarker to guide immunotherapy decisions for patients with cancer". One million bases or one Mb is considered the standard by experts for TMB analysis, considering that this amount of DNA sequence corresponds to approximately 300 genes, CMS' decision to crosswalk to 81445 greatly undervalues the work and resources needed to perform an accurate analysis of TMB.

Microsatellite Instability (MSI) testing looks at DNA microsatellites from the tumor sample to detect replication errors[6]. Reliable assessment of MSI by sequencing methods requires evaluation of sufficient microsatellite loci that is typically only achievable with larger panels, i.e., those in excess of 50 genes.

AMP urges CMS not to finalize the preliminary determinations for CPT codes 8X017, 8X018, 8X019, 8X020, 8X021, and 8X022 as it would have a significant and negative impact on patient access and AMP member laboratories. **AMP urges CMS to adopt AMP's recommendation from the Annual Laboratory Meeting outlined in table 1.** We thank you for the opportunity to submit comments on the CY 2024 CLFS preliminary pricing determinations and remain committed to working with you to ensure accurate pricing and secure patient access to laboratory tests. Should you have any questions about our recommendations, please direct your correspondence to Annie Scrimenti, Associate Director of Public Policy and Advocacy, at ascrimenti@amp.org.

Sincerely,

Jay Patel, MD
Co-Chair: AMP Economic Affairs Committee, Vice Chair: New Codes and Pricing Subcommittee

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[4] Stenzinger A, Allen JD, Maas J, Stewart MD, Merino DM, Wempe MM, Dietel M. Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. Genes Chromosomes Cancer. 2019 Aug;58(8):578-588. doi: 10.1002/gcc.22733. Epub 2019 Mar 7. PMID: 30664300; PMCID: PMC6618007.

[5] Aggarwal C, Ben-Shachar R, Gao Y, Hyun SW, Rivers Z, Epstein C, Kaneva K, Sangli C, Nimeiri H, Patel J. Assessment of Tumor Mutational Burden and Outcomes in Patients With Diverse Advanced Cancers Treated With Immunotherapy. JAMA Netw Open. 2023 May 1;6(5):e2311181. doi: 10.1001/jamanetworkopen.2023.11181. PMID: 37129893; PMCID: PMC10155064.

[6] https://www.cdc.gov/genomics/disease/colorectal_cancer/MSI.htm#:~:text=Microsatellites%20are%20regions%20of%20repeated,as%20a%20measure%20of%20instability