October 25, 2023

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

RE: 2024 CLFS Preliminary Determinations
Submitted electronically via CLFS_Annual_Public_Meeting@cms.hhs.gov

Dear Administrator Brooks-LaSure:

On behalf of BLOODPAC, thank you for the opportunity to review and comment on preliminary payment determinations specific to the CY2024 clinical laboratory fee schedule (CLFS).

BLOODPAC is a public-private consortium that develops standards and best practices, organizes and coordinates research studies through its members, and operates a data commons to support the liquid biopsy research community.

We define a liquid biopsy as a molecular test performed on a sample of blood, urine, or other body fluid, to look for signals associated with cancer, such as circulating tumor cells, DNA, RNA, or proteins. Liquid biopsy use cases vary, and may include:

- Detecting cancer at an early stage
- Informing treatment with targeted therapies, based on presence or absence of specific mutations
- Determining treatment efficacy and/or cancer recurrence (e.g., relapse or minimum/molecular residual disease)

Our mandate at BLOODPAC is to accelerate the development, approval and accessibility of liquid biopsy assays to improve the health outcomes of patients with cancer. We do this via an unprecedented collaborative consortium infrastructure of over 60 members comprising industry, academia, and regulatory agencies.

Specific to the 2024 CLFS, our concerns and comments lie with pricing recommendations for the three new genetic sequencing procedures (GSP) codes which use cell-free DNA as the specimen type: 8x020, 8x021, and 8x022.[1]

We support the original crosswalks as submitted by the Association for Molecular Pathology (AMP), the College of American Pathologists (CAP), ACLA, AdvaMed, and other public commenters.

The proposed crosswalks were as follows:

Code	Descriptor	ACLA/AdvaMed proposed crosswalk
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	81455 * 1.25
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	81455 * 1.25
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	0244U * 1.25

The CDLT advisory panel voted unanimously to affirm the recommended crosswalks for 8x020 and 8x021. For 8x022, the minority panel voted to affirm the crosswalk to 0244U * 1.25. Importantly, these codes were constructed with escalating resource requirements to perform the service versus their tissue-based counterparts. Pricing each of the codes at the same price defeats the intended purpose of these codes and devalues the significant resources required to perform Tumor Mutational Burden (TMB).

Plasma sequencing is more resource intensive than tissue-based samples, when performing somatic testing

A 1.25 multiplier is appropriate when a test performed on a plasma specimen is crosswalked to an otherwise comparable code for a test performed on formalin-fixed paraffin-embedded (FFPE) tumor tissue.

Compared to tissue, plasma requires more complex sequencing, raw materials and bioinformatics to call the same clinically relevant biomarkers accurately. Plasma has more “noise” to filter out to identify mutations in a few strains of circulating tumor DNA, compared to specimens taken directly from tumor tissue biopsies. To account for the complexities of plasma specimen sequencing and to provide accurate and reliable results, laboratories must sequence plasma specimens at a deeper range, with longer sequencing time, and develop, validate, and employ sophisticated algorithms for the same variant detection.

Below is an illustration from Illumina which both describes the overall costs of NGS-based panel sequencing, and the relative increase in costs for plasma-based samples, versus tissue-based samples.

Testing cost category	Tissue-based 523-gene assay DNA and RNA	Plasma-based 523-gene assay DNA	Multiplier (Plasma vs. Tissue-based)
NGS core consumables	$700	$1,328	
NGS library preparation consumables	$737	$499	
Non-NGS reagents, instrument amortization, labor and other costs	$595	$725	
Overhead	$610	$766	
Total costs	$2,642	$3,318	1.26

Source: NGS reagents cost based on US list prices available at Illumina.com, other costs assessed in internal Illumina cost evaluation, overhead estimated at 30% of total costs.

8x022 includes Tumor Mutational Burden (TMB), which inherently requires a large panel to support broad tumor profiling, and it should be priced as such. CPT 8x022 references tumor mutational burden (TMB) in its descriptor. As reported by Friends of Cancer Research in their 2021 manuscript *Aligning tumor mutational burden (TMB) quantification across diagnostic platforms: phase II of the Friends of Cancer Research TMB Harmonization Project,*[2] "Panel sizes greater than 667Kb are necessary to maintain adequate positive percent agreement (PPA) and negative percent agreement (NPA) for calling TMB high versus TMB low across the range of cutoffs used in practice."

This study examined 16 participating diagnostic NGS panel assays reporting TMB, and the number of genes used ranged from a low (324 genes) to high (649 genes). These are all comprehensive panels. Therefore, the inclusion of TMB inherently supports that these are large panel assays, with significant costs to validate and perform.

TMB and Microsatellite Instability (MSI) play important roles in the management of patients with advanced cancers. These are included in code descriptors 8x021 (MSI) and 8x022 (TMB + MSI) and their value should be recognized.

The National Comprehensive Cancer Network (NCCN) publishes guidelines[3] which identify key genes and specific positions that have clinical utility in somatic mutation testing. These data are segmented by indication, by stage, by use case (predictive, prognostic), and by category (1, 2A, 2B, emerging). NCCN guidelines are frequently used by commercial payers[4] to inform coverage policy; they were also cited by National Government Services as the basis for Comprehensive Genomic Profiling assay content and coverage requirements.

Within the Indications and Limitations of Coverage section, Local Coverage Determination #L37810 (*Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms*) specifies "the genes and genomic positions required are listed in Category 1 or 2A of the most current version of the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium[5]."

TMB and MSI are present in NCCN Guidelines among several cancer indications and eligible therapies:

Category	Indications Noted (level 1 or 2A)	Corresponding Therapies
MSI	12	41
TMB	15	12

These include the following cancers (**bold** indications are limited to only MSI coverage):

NCCN-Bone Cancer	NCCN-Neuroendocrine and Adrenal Tumors
NCCN-Breast Cancer	NCCN-Ovarian Cancer
NCCN-Cervical Cancer	**NCCN-Pancreatic Adenocarcinoma**
NCCN-Colon Cancer	NCCN-Prostate Cancer
NCCN-Esophageal and Esophagogastric Junction Cancers	**NCCN-Rectal Cancer**
NCCN-Gastric Cancer	NCCN-Testicular Cancer
NCCN-Head and Neck Cancers	NCCN-Uterine Neoplasms
NCCN-Hepatobiliary Cancers	

CMS has recently applied more appropriate prices to cell-free DNA assays.

CPT/PLA code	0179U	0326U	N/A
Test Name	Resolution ctDx Lung™	Guardant360®	Liquid Hallmark
Lab/Manufacturer	Resolution Bioscience, Inc	Guardant Health, Inc	Lucence Health, Inc.
Number of genes reported	23	83 or more	80
Sequence variants	X	X	X
CNVs	X	X	X
Rearrangements	X	X	X
MSI		X	
TMB		X	
CLFS price	$1,943.21	$5,000*	$2,242.16**

* Preliminary CY 2024 pricing proposed by CMS

**Priced via Palmetto GBA's MolDX program

On behalf of BLOODPAC, we urge CMS to address these issues and not finalize the 2024 CLFS as drafted. **We ask that CMS reconsider each of the crosswalks supported by medical and trade association and the CDLT Advisory Panel recommendations. At minimum, we urge the CLFS team to recommend gapfill for these three codes in 2024.**

We appreciate your consideration of our comments. Should you have any questions or require our expertise, please direct your correspondence to me at lauren@BLOODPAC.org.

Respectfully,

Lauren C. Leiman
Executive Director
BLOODPAC

[1] https://www.cms.gov/medicare/payment/fee-schedules/clinical-laboratory-fee-schedule-clfs/annual-public-meetings

[2] Vega, DM et al: Aligning tumor mutational burden (TMB) quantification across diagnostic platforms: phase II of the Friends of Cancer Research TMB Harmonization Project
DOI:https://doi.org/10.1016/j.annonc.2021.09.016

[3] https://www.nccn.org/guidelines/category_1

[4] CIGNA:
https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0520_coveragepositioncriteria_tumor_profiling.pdf
UnitedHealthcare: https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/molecular-oncology-testing-for-cancer.pdf

[5] https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37810&ver=17