



20 West Kinzie Street
Chicago, Illinois 60654
info@BLOODPAC.org

October 24, 2022

Rasheeda Arthur, Ph.D.
Karen Nakano, M.D.
Center for Medicare
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: 2023 CLFS Preliminary Determinations
Submitted electronically

Dear Dr. Arthur, Dr. Nakano, and the CLFS team:

On behalf of the BLOODPAC Consortium, thank you for the opportunity to review and comment on the CY2023 Clinical Laboratory Fee Schedule (CLFS) Preliminary Determinations.

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.

Based on the CY2023 preliminary determinations that CMS has put forth, we believe there are opportunities to improve this process as described in SSA section 1834A and 42 CFR 414.508(b) and we have provided specific examples below to illustrate this. The three key policy and process issues that we would like to address are:

1. CMS electing to disregard the CDLT Advisory Panel recommendations
2. The selection of broad category codes as the most appropriate crosswalk when there are more discrete options with comparable and well-defined methodology and resource use
3. Liquid biopsy tests and tissue-tests have vastly different methodologies not adequately described by the same code

CMS should provide a clear rationale when disagreeing with the CDLT Advisory Panel

In the CY2023 preliminary pricing decisions, CMS disagreed with the CDLT Advisory Panel recommendation over 40% of the time and, in 21% of those instances, the CDLT Advisory Panel vote was 12-0.

In cases where CMS disagreed with the majority Advisory Panel proposal, CMS proposed their own determination 26% of the time and 18% of the time, CMS selected a proposal that received a minority of votes.

We understand that CMS reserves the right to disagree and propose different determinations, but this represents a significant departure from expert opinion. The Advisory Panel is comprised of KOLs from a broad spectrum of pathology backgrounds, and we find the frequency at which CMS disagrees with the Advisory Panel to be concerning. When CMS disagrees with the panel, we urge CMS to put forth a clear rationale as to why the proposed determination was overruled. The rationales CMS currently provides are vague and fail to provide insight as to why CMS did not follow the panel recommendation:

“The cross walked code(s) appear to use similar methods and resource utilization.”



Providing a more detailed rationale would help stakeholders understand why CMS believes that the code they selected is more appropriate than the Advisory Panel's choice and would help stakeholders better address differences in methodology and resources for the proposed codes during the June/July open meetings, the fall open comment period, and in future submissions. CMS should not select a broad category code as the most appropriate crosswalk when a more comparable code is available on the CLFS

BLOODPAC feels that CMS has been defaulting to broad category codes when there are far more appropriate options in the PLA code set. When there are codes for a specific service that has discrete lab methods and resource utilization, they should be used over a category code. In general, codes such as 81445, 81450 and 81455 should be the crosswalk of last resort. All three of these codes define a very broad category of services that have a wide range of resource requirements related to delivering these services.

For instance, 81455 can be services that are DNA based, or DNA and RNA based. It also can include copy number variations and fusions, or it can exclude these services. As a result, there are a wide variety of services which could bill with this code making a methodology and resource comparison very challenging. The difference in resources and methodologies between RNA and DNA analyses alone is very large. As a result, meeting the statutory requirement of "comparable" is next to impossible when there is a more specific assay on the fee schedule with a defined and comparable methodology and resource utilization.

There were a few instances in the Preliminary Determinations that serve as clear examples of cases where broad category codes were selected when more comparable crosswalks are available:

One example is 0326U. The public proposed that this code, which describes a proprietary liquid biopsy test, be crosswalked to another proprietary liquid biopsy test, 0242U, produced by the same company. The Advisory Panel voted 12-0 to crosswalk in favor of this crosswalk. 0326U and 0242U are essentially identical in every way and use patented and proprietary techniques equivalently across both tests. 0326U is the next version of 0242U. It is simply a slightly larger panel of 0242U, meaning it actually uses slightly more resources. However, CMS choose to crosswalk 0326U to 81455. Given that it is an almost identical test, 0242U is a better crosswalk for 0326U than a non-specific code like 81455.



Liquid biopsy tests and tissue-tests have vastly different methodologies not adequately described by the same code CMS has proposed to crosswalk 0326U, a liquid biopsy test, to 81455, which is generally a tissue-based code. The 81455 code was created in 2015, but the AMA constructed this code in 2014. At that time there was no blood-based assays on the market. 2015 CPT Changes: An Insider's View, published by the AMA, includes a Clinical Example of how 81455 is intended to be used and a Description of the Procedure. The Description of the Procedure clearly states that DNA is intended to be isolated from the patient's tumor tissue.

There are several ways in which the methodologies of tissue and liquid-based tests differ. The pre-sequencing work methodology for blood samples is substantially different than that of a tumor tissue sample. For a blood sample, the blood must be spun down to separate the plasma and then the cfDNA and ctDNA is extracted from the plasma by size selection to only obtain the DNA of interest. A major challenge with a blood-based assay is finding the very small fraction of ctDNA amongst the very large population of normal cfDNA from healthy cells that are shedding DNA.

The sequencing depth also varies drastically between these sample types. A liquid biopsy assay may require deeper sequencing which is dependent upon the assays performance to ensure that the DNA is from a tumor as opposed to normal healthy tissue. Tissue based tests do not require such a depth of sequencing since the tumor tissue is significantly enriched already and the length of the fragment is inherently longer.

Finally, the bioinformatics from the raw sequencing is far more complicated in blood-based testing compared to tissue. The healthy cell cfDNA occurs at a far greater proportion in DNA derived from the blood, creating significant noise and extensive computational work. To reduce this noise, liquid biopsy tests employ sophisticated algorithms. These more resource intensive approaches are not required in direct tumor tissue sequencing since noise from healthy tissue is not present at the same level.

Given the above examples of the vast differences in methodologies between liquid and tissue-based tests, liquid biopsy tests should not be cross walked to 81455 unless there is an absence of a more appropriate code on the CLFS. This is not the case for the previously discussed example of 0326U. In summary, we request that CMS provide a more specific and detailed rationale when they disagree with the majority opinion of the Advisory Panel and refrain from using unspecific codes like 81445, 81450, and 81455 when the public and the Advisory Panel recommends a more appropriate discrete code.



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,

A handwritten signature in black ink that reads 'Lauren Leiman'.

Lauren Leiman

Executive Director

BLOODPAC Consortium