November 13, 2021

VIA Electronic Submission to PartBLCDComments@anthem.com

National Government Services Medical Policy Unit
P.O. Box 7108
Indianapolis, Indiana 46207-7108

RE: Proposed LCD - Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (DL37810)

To Whom It May Concern:

On behalf of the Coalition for 21st Century Medicine (C21), we appreciate the opportunity to submit comments regarding the above-captioned proposed Local Coverage Determination (LCD).

C21 comprises many of the world's most innovative diagnostic technology companies, clinical laboratories, physicians, venture capital companies, and patient advocacy groups. C21's mission is to improve the quality of health care by encouraging research, development, and commercialization of innovative diagnostic technologies that will personalize patient care, improve patient outcomes, and substantially reduce health care costs. For 15 years, C21 has worked with the Centers for Medicare and Medicaid Services (CMS) and Medicare contractors on the development, promulgation, and implementation of coverage policies intended to facilitate appropriate Medicare reimbursement for high-quality clinical laboratory tests.

C21 member companies currently offer and/or are actively developing next generation sequencing (NGS)-based comprehensive genomic profiles (CGPs) for patients with advanced cancer. Given C21's mission to facilitate the development and commercialization of innovative diagnostics, C21 has a keen interest in National Government Services' consideration of the above-captioned proposed LCD.

C21 strongly supports the proposed LCD insofar as it would expand coverage for NGS-based CGPs offered as laboratory-developed tests (LDTs), as permitted under National Coverage Determination (NCD) 90.2.[1] As noted in the proposed LCD, utilization of NGS-based CGPs is well-supported in clinical guidelines, both as a means to identify individual gene variants[2] as

[1] Centers for Medicare & Medicaid Services, NCD - Next Generation Sequencing (NGS) 90.2 (accessed Oct. 26, 2021), *available at* https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=372.

[2] *See, e.g.,* National Comprehensive Care Network, NCCN Guidelines Version 6.2021: Non-Small Cell Lung Cancer (Sept. 30, 2021) ("To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *EGFR* mutations, *BRAF* mutations, *METex14* skipping mutations, *RET*

well as a mechanism to identify driver mutations (i.e., tumor mutational burden (TMB) for assessment of response to immune checkpoint inhibitors (ICI)).[3] Accurate measurement of TMB is generally understood to require the sequencing of hundreds of genes via NGS.[4]

That being said, C21 believes the proposed LCD would benefit from certain targeted modifications and/or clarifications. To that end, C21 offers the following comments for National Government Services' consideration:

- **Recommended deletion of language limiting coverage for NGS-based CGPs to situations where "more limited (e.g., individual analyte or targeted panel (5-50 genes) testing is insufficient".** The proposed LCD currently states that NGS-based CGPs are only reasonable and necessary when "more limited (e.g., individual analyte or targeted panel (5-50 genes)) testing is insufficient . . ." However, a doctor may reasonably decide that testing with an NGS-based CGP is medically necessary instead of running a more targeted panel, particularly insofar as tumor tissue may be limited, or opting for a single assay that assesses hundreds of genes (including relevant cancer biomarkers) provides information more efficiently than multiple targeted tests. Furthermore, "individual analyte or targeted panel testing" is never sufficient to accurately measure TMB, which NCCN guidelines recognize as a key input for predicting response to treatment with ICIs across a number of different cancers (e.g., bone, breast, cervical, esophagus, gastric, nasopharyngeal, salivary gland, occult primary, ovarian, testicular, thyroid, endometrial, uterine, vulvar). As such, C21 recommends that National Government Services delete the above-quoted language from the final LCD.

  Alternatively, if National Government Services decides to retain the "insufficient" language, C21 strongly recommends that National Government Services revise the LCD to clarify – using specific, objective criteria – when more limited testing would be considered "insufficient". The proposed LCD language does not currently offer ordering providers or performing clinical laboratories any concrete guidance on how to determine when targeted testing is "insufficient". This lack of clarity may cause confusion among ordering providers and complicate treatment decisions for patients with limited time to mitigate rapidly progressing diseases, and may cause issues in post-payment audits, where laboratories will be expected to produce documentation supporting a determination of "insufficiency".

- **Recommended modification of minimum requirements to establish analytical validity.** C21 agrees that only those NGS-based CGPs with established evidence of

rearrangements, *ALK* fusions, and *ROS1* fusions. Both FDA and laboratory-developed test platforms are available that address the need to evaluate the need to evaluate these and other analytes.")

[3] *See, e.g.,* National Comprehensive Cancer Network, NCCN Guidelines Version 8.2021: Breast Cancer (Sept. 13, 2021) (recommending the use of pembrolizumab in patients with any breast cancer subtype, and TMB-high as measured via NGS (NCCN Category of Evidence 2A, Category of Preference "Useful in certain circumstances").

[4] *See* Buchhalter I, Rempel E, Endris V, et al. Size matters: Dissecting key parameters for panel-based tumor mutational burden analysis. *Int J Cancer*. 2019;144(4):848-858 ("[Ou]r data suggest that panels between 1.5 and 3 Mbp are ideally suited to estimate TMB with small CIs, whereas smaller panels tend to deliver imprecise TMB estimates for low to moderate TMB (0–30 muts/Mbp), connected with insufficient separation of hypermutated tumors from non-hypermutated tumors.")

analytical validity should be eligible for coverage under the final LCD. However, the proposed LCD currently provides that laboratories offering LDTs must have "published, peer-reviewed studies" – plural – to be eligible for coverage.

It would be highly unusual for a clinical laboratory to have multiple peer-reviewed publications establishing analytical validity of an assay. While analytical validity might be addressed in a single publication, the focus of most publications is on clinical validity and/or clinical utility. As such, we encourage National Government Services to consider a single published, peer-reviewed study addressing analytical validity to be sufficient to establish the analytical validity of an NGS-based CGP.

Furthermore, peer-reviewed publications are not the only way that a clinical laboratory can establish the analytical validity of an LDT. For example, the New York State Department of Health currently requires laboratories that offer NGS-based CGPs as LDTs to go through a test-specific approval process before analyzing specimens from New York. This process entails the evaluation of key analytical performance characteristics (e.g., sensitivity, specificity, precision, reproducibility), including requiring that the performance characteristics of such assays be established and validated for each type of variant detected by the assay (e.g., SNVs, insertions, deletions, copy number gains and losses, structural variants, MSI, and/or TMB) and for each type of sample analyzed.[5] Because favorable review by the New York State Department of Health would provide an objective, reputable third-party assessment of an assay's analytical validation, we encourage National Government Services to clarify that NYS approval would also be sufficient to establish the analytical validation of NGS-based CGPs offered as LDTs.

- **Recommended deletion of language suggesting that NGS-based CGPs performed on blood specimens are not eligible for coverage under the LCD.** The proposed LCD notes that its scope is "specific to solid tumors and exclusive of hematologic malignancies, circulating tumor DNA testing, and other cancer related uses of NGS, such as germline testing." It is unclear whether the reference to "circulating tumor DNA testing" is intended to restrict coverage to NGS-based CGPs for solid tumors that are performed on a blood specimen, or if this language is intended to address circulating tumor DNA tests offered solely in a screening population (i.e., in patients who have not already been diagnosed with cancer).

  C21 strongly supports the eligibility of NGS-based CGPs run on blood specimens from patients already diagnosed with cancer for coverage under the LCD, and encourages National Government Services to remove the language suggesting that liquid biopsies are ineligible for coverage.

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[5] New York State Dep't of Health, Oncology – Molecular and Cellular Tumor Markers: Next Generation Sequencing (NGS) guidelines for somatic genetic variant detection (April 2021), https://www.wadsworth.org/sites/default/files/WebDoc/NextGenSeqONCOGuidelines%20_April_2021.pdf.

C21 thanks National Government Services for the opportunity to comment on the proposed LCD and encourages National Government Services to continue prioritizing the evaluation of new diagnostic technologies, including NGS-based CGPs, where supported by clinical evidence. For your reference, we have attached an appendix that illustrates our proposed revisions to the draft LCD.

Thank you for considering our comments. Please contact me at hmurphy@c21cm.org should you have any questions or if we can provide you with further information.

Sincerely,

Hannah Murphy
Executive Director
The Coalition for 21st Century Medicine

Appendix – Proposed Revisions to Proposed LCD Language

Coverage Guidance

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Next-Generation Sequence (NGS) Comprehensive Genomic Profile (CGP) Testing

Indications and Limitations of Coverage

This policy section describes coverage of NGS CGP diagnostic testing for patients with advanced cancer as allowable by a Medicare Administrative Contractor (MAC) under the National Coverage Determination (NCD) 90.2 (1). The policy scope is specific to solid tumors and exclusive of hematologic malignancies, ~~circulating tumor DNA testing (ctDNA),~~ and other cancer-related uses of NGS, such as germline testing.

CGP is a NGS approach that uses a single assay to assess hundreds of genes including relevant cancer biomarkers, with solid evidentiary support for clinical utility in guidelines and clinical trials. CGP assays include not only individual genetic variants (single nucleotide variants (SNVs), insertions/deletions (INDELs), copy number alterations (CNAs), structural variants (SVs), and splice-site variants), but also patterns of mutations such as DNA mismatch repair deficiency (dMMR), microsatellite instability (MSI), and total mutational burden (TMB). CGP testing may also include RNA sequencing to detect structural rearrangements, such as fusions/translocations and functional splicing mutations.

CGP NGS testing for patients with advanced cancer is reasonable and necessary ~~only~~ when ~~more limited (e.g., individual analyte or targeted panel (5-50 genes)) testing is insufficient;~~ the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient has:

- either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
- not been previously tested with a CGP for the same cancer genetic content; and
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy)

Additionally, the test performed must be able to detect at least the minimum genes and genomic positions required for the identification of clinically supported, FDA-approved therapies. The genes and genomic positions required are listed in Category I or 2A of the most current version of the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium (2). Testing assays must be FDA approved, or if a laboratory developed test (LDT), have one published, peer-reviewed ~~studies~~ study supporting analytic validity or approval by the New York State Department of Health.