November 11, 2021

Dr. Greg McKinney
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Re: Proposed dLCD: National Government Services: Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (DL37810)

Submitted electronically to: PartBLCDComments@anthem.com

Dear Dr. McKinney:

The Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) appreciate the opportunity to provide comments on National Government Services' draft local coverage determination (dLCD) for Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (DL37810).

AMP is an international medical and professional association representing approximately 2,500 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government, and the in vitro diagnostics industry.

The CAP is the world's largest organization of board-certified pathologists and the leading provider of laboratory accreditation and proficiency testing programs. The CAP serves patients, pathologists and the public by fostering and advocating for excellence in the practice of pathology and laboratory medicine worldwide.

We appreciate that National Government Services has proposed to expand coverage of next-generation sequence (NGS) comprehensive genomic profile (CGP) testing for advanced solid tumor cancers. We commend National Government Services for recognizing the clinical value of NGS CGP for certain patients. However, AMP and CAP are concerned that the draft policy as written is unclear and may limit proper access to molecular services. We offer the following comments that will ensure appropriate access to panel testing for Medicare beneficiaries with cancer.

Indications and Limitations of Coverage

Publication of Analytical Validity for Laboratory Developed Tests

AMP and the CAP are concerned about the proposed policy's requirement that "testing assays must be FDA approved, or if a laboratory developed test (LDT), have published, peer-reviewed studies supporting

analytic validity." Regulatory requirements stipulated in the Clinical Laboratory Improvement Amendments (CLIA) already provide strict validation requirements that must be followed before an assay can be offered to patients. CLIA also requires quality assurance and proficiency testing by federally approved programs for these assays. These tests meet or exceed CLIA standards, and/or other federal, state (e.g., NYSDOH clinical laboratory evaluation program), and professional practice standards, as well as provide clinically significant information to patients. Many have been demonstrated to be of highest quality by peer review through the College of American Pathologists (CAP) laboratory inspection and proficiency testing processes.

A number of studies have been published which examined CAP proficiency testing results to assess accuracy of NGS testing across laboratories and all found laboratories demonstrated overall excellent performance for detecting variants of interest (Kim et. al. 2018; Nardi et. al., 2021; Surrey et al., 2019; and Merker et al., 2019). For example, a 2019 publication examined proficiency testing data from the CAP next generation sequencing solid tumor survey on laboratory performance found that 111 laboratories demonstrated an overall accuracy of >98% with high specificity when examining 10 clinically relevant somatic single-nucleotide variants (SNVs) with a variant allele fraction of 15% or greater (Merker et. al., 2019). Moreover, multiple publications have examined the reliability of numerous commercial assays, such as the Oncomine Comprehensive Assay, that are utilized by laboratories as laboratory developed tests (see Commercial assay references below). Thus, mandating publication of peer-reviewed studies as a condition to coverage is burdensome and duplicative to existing requirements under CLIA and third-party accreditors, such as CAP and New York State. **AMP and CAP recommend that this requirement be removed from the policy.**

Defining "Insufficient"

We are concerned that, as written, the policy may promote increased usage of larger panels when, in some instances, 5-50 gene panels may be sufficient. The policy states, "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." **AMP and the CAP seek clarification on how National Government Services are defining "insufficient" for purposes of the coverage policy.** As written, it is unclear when CGP should be utilized versus targeted panels.

AMP and CAP recognize that comments on this draft are limited to only the NGS CGP testing section. However, the policy as written appears to only provide coverage for 5-50 gene panels for non-small cell lung cancer (NSCLC) and metastatic colorectal cancer (mCRC) and does not recognize that there are additional solid tumor malignancies where a 5-50 gene panel may be sufficient and necessary. For example, patients with cutaneous melanoma are eligible for checkpoint immunotherapy (e.g., pembrolizumab) without PDL1, MSI/dMMR or TMB testing, but may require a 5-50 gene panel containing BRAF, NRAS, KIT, NTRK1, NTRK2 and NTRK3 to identify second line systemic therapy for metastatic or unresectable disease (i.e., BRAF testing for dabrafenib, KIT testing for Imatinib, NRAS testing for Binimetinib, or NTRK testing for Larotrectinib) (NCCN guidelines Cutaneous Melanoma, Version 2.2021). **In order to ensure that this policy appropriately covers gene panel testing, we request that National Government Services consider opening for comment the entire coverage section. Should AMP and CAP need to request reconsideration for this to occur, please advise so we can proceed accordingly.**

Alignment with NCCN Biomarker Compendium

AMP and the CAP have been very supportive of coverage policies that work to align their coverage

parameters with clinical practice guidelines, such as those published by AMP and CAP, as well as guidelines from National Comprehensive Cancer Network (NCCN). However, any such requirements should allow time for adjustments to be made to any CGP test. For example, the addition of a new biomarker could potentially invalidate a clinical assay. **AMP and the CAP recommend that this requirement be refined to ensure that National Government Services would allow clinical laboratories sufficient time to prepare or re-validate an assay if a new biomarker were to be added to the NCCN compendium.** For example, it may be helpful for the policy to define a date with regards to which version of the NCCN is indicated, in order for laboratories to better understand the requirements.

Exclusion of ctDNA from Policy Scope

The draft policy states, "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." **AMP and CAP request that ctDNA be removed as a limitation of coverage as, ctDNA can be used to assess solid tumors, especially in cases with insufficient tissue obtained, or if the patient is unable to undergo a procedure to obtain the tumor sample.**

Utilization Guidelines

In the billing and coding article DA5686 that accompanies the dLCD, the utilization guidelines state, "Regarding Next-Generation Sequencing (NGS) Comprehensive Genomic Profile (CGP) Testing, any molecular procedure CPT code other than 81455 that is submitted on the same day of service as 81455 will be automatically denied as not medically necessary." **AMP and the CAP are concerned that this guideline may have detrimental effects on patient care in certain circumstances and request that this guideline be removed.**

Tests that are coded under CPT code 81455 can be extremely heterogeneous in size and composition. While some larger panels are capable of assessing things like microsatellite instability, copy number, and tumor mutational burden, it is incorrect to assume that all assays under the CPT code 81455 designation have the same capabilities. In situations where a single large panel (i.e., 50 or more genes) does not contain all the genes or genomic assessments needed, a separate procedure may need to be performed by the laboratory. Some laboratories assess key genes or genomic regions with procedures that are separate from their panel. For example, some laboratories assess MSI/MMR testing separately from the panel. When assessing glioma tumor samples, copy number evaluation is assessed and performed separately from NGS panel (NCCN Guidelines, Central Nervous System Disorders, Version 2.2021). There are also rare instances where the CPT code 81455 would need to be billed twice for a patient, such as when a patient is presenting with two different primary cancers, both resected at the same time. In these instances, allowance for billing of more than one procedure beyond CPT code 81455 may be needed. Furthermore, NCCI edits allow for PTP edits of 1 for 81455 and many molecular codes. Therefore, the proposed policy mandate conflicts with NCCI policy, which will cause additional confusion for laboratories.

ICD-10 Codes

The billing and coding article also lists the ICD-10 diagnosis codes that are considered medically necessary in the treatment of solid organ neoplasms. The proposed policy includes diagnosis codes for patients with advanced primary cancer. Since advanced cancers often spread to other parts of the body, the policy should include diagnosis codes for **both** primary and secondary malignant neoplasms.

Therefore, AMP and CAP recommend that the following additional ICD-10 codes be added to the policy so that coverage applies to secondary neoplasms of these sites:

C79 – Secondary malignant neoplasm of other specified sites
C79.0 – Kidney and renal pelvis
C79.1 – bladder and other and unspecified urinary organs
C79.2 – Skin
C79.3 – Brain and cerebral meninges
C79.4 – other and unspecified parts of nervous system
C79.5 – Bone and bone marrow
C79.6 – Ovary
C79.7 – Adrenal gland
C79.8 – Other specified sites
C79.9 – unspecified cite

Thank you again for the opportunity to review and comment on this proposed policy. We are happy to provide you with additional clinical or other information to assist you as you finalize this draft LCD. Please direct your correspondence to Tara Burke, Senior Director of Public Policy and Advocacy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology

College of American Pathologists

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