June 20, 2019

Palmetto, GBA
Part B Policy
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RE: MolDX: Next-Generation Sequencing for Solid Tumors (DL38045)

Dear Dr. Bien-Willner,

Thank you for the opportunity to comment on Palmetto's proposed coverage policy for Next Generation Sequencing (NGS) for Solid Tumors (DL38045).

The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 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 the government, academic medicine, private and hospital-based clinical laboratories, and the *in vitro* diagnostics industry.

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

We are submitting a joint comment letter because both our organizations are fully aligned in our views regarding this draft Local Coverage Determination (dLCD). We appreciate Palmetto's willingness to provide limited coverage for NGS-based testing of solid tumors in cancer patients as part of emerging efforts to both improve detection of cancer and help guide treatment decisions and we respectfully ask that you consider our following recommendations.

**1. <u>Criteria for Coverage</u>**

**A. dLCD statement:** The Criteria for Coverage section states that all the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
  - the patient has either:
    - Recurrent cancer
    - Relapsed cancer
    - Refractory cancer
    - Metastatic cancer
    - Advanced cancer (stages III or IV)
  - AND has not been previously tested by the same test with the same primary diagnosis
  - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes at least the minimum genes and genomic positions required for the identification of all FDA-approved therapies with a companion diagnostic biomarker for its intended use

that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in an associated Coverage Article, as well as in the MolDX TA forms.

**Comment:** There are multiple clinical scenarios whereby repeat testing of the same cancer is necessary, typically as the cancer evolves to evade front-line targeted therapy. Specifically, relapsed, recurrent and metastatic cancers under pressure by treatment often show losses and gains in mutations compared to the primary tumor, rendering them, in effect, new cancers.

In its Decision Memo for Next Generation Sequencing (NGS) for Medicare beneficiaries with advanced cancer (CAG-00450N), dated March 16, 2018, CMS states that repeat testing is allowed under certain circumstances. Any lab diagnostic tests using NGS that are FDA approved/cleared as a companion diagnostic are nationally covered (i.e., no contractor discretion) under this NCD, *and coverage determinations for the rest of the diagnostic lab tests using NGS will be made by Medicare Administrative Contractors. If the patient has not been diagnosed with a new cancer, diagnostic lab testing using NGS is coverable but only if when a different diagnostic lab test is furnished from what was furnished previously* (emphasis added)."

**Recommendation:** Palmetto should consider coverage for repeat NGS testing when the subsequent post-treatment cancer is recurrent, relapsed, treatment-refractory or metastatic.

**B. dLCD statement:** The second sub-bullet under "reasonable and necessary" Criteria for Coverage states: "AND has not been previously tested by the same test with the same primary diagnosis".

**Comment:** In the Criteria for Coverage section under "Situations in which a test should not be used or when coverage is denied", the proposed policy states that "the test in question will not be covered if another CGP test was performed on the same tumor specimen (specimen obtained on the same date of service).

**Recommendation:** To provide for clarity and uniformity, we recommend that the second sub-bullet under "reasonable and necessary" criteria for coverage be amended as follows:

> "and has not been previously tested on the same tumor specimen with the same primary diagnosis *on the same date of service*".

Alternatively, an additional bullet could be added to "Criteria for Coverage" that states:

> "Repeat NGS testing on the same patient for the same primary diagnosis may be reasonable and necessary when performed on a different date of service."

**C. dLCD statement:** The third bullet point under Criteria for Coverage states, "The assay performed includes at least the minimum genes and genomic positions required for the identification of ***all*** (emphasis added) FDA-approved therapies with a companion diagnostic biomarker for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in an associated Coverage Article, as well as in the MolDX TA forms."

**Comment:** The companion diagnostic space is rapidly evolving and under Palmetto's proposed policy CLIA labs would be required to update their assay frequently (re-validate) or adopt a broader "future-proof" assay. Clinical laboratories often want to take a modular approach to assay adoption. Having multiple assays that address companion diagnostic biomarkers allow labs to "pick-and-choose" based on relevant clinical indications and/or serialize testing based on prevalence, with the goal to maximize tissue availability and reduce testing cost per patient.

**Recommendation:** We recommend that Palmetto substitute the word "all" with "clinically relevant".

**3. Technical Assessment (TA) Checklist (M00151, V5)**

**TA statement:** The first two questions under the "Test Details Checklist/Questionnaire" section of the Technical Assessment (TA) document ask:

> 1. Does this test result in a report/information that is limited to providing patient genetic/genomic information and ancillary data that are not proprietary, utilizing methodologies for which Clinical Validity (CV) and Clinical Utility (CU) are well established in the literature?
>
> 2. Is this a test based on novel/proprietary technology or algorithms, and/or provides a result based on such technology or algorithms? If yes, Clinical Validity and Clinical Utility must be described.

**Comment:** Questions #1 and #2 appear to be an attempt to clearly distinguish NGS-based tests that have proven clinical utility (CU) and clinical validity (CV) from those that do not. Most lab-developed NGS-based procedures, to the contrary, have some components of CV/CU that arise from literature-supported evidence and other components of CV/CU that are supported by unpublished novel or proprietary lab-specific algorithms or data. Most lab-developed NGS-based procedures therefore fall somewhere in the middle of the two options offered in the TA.

Additionally, while Palmetto has taken efforts to streamline its technical assessment checklist the document still appears to be overly burdensome for test applicants and lacking in transparency. For example, the checkboxes do not include information about the way in which the yes/no responses could impact and inform Palmetto's ultimate coverage decision.

**Recommendation:** We recommend that Palmetto increase transparency regarding its evaluation and response to the questions and other information required under the TA document that is used by MolDX to evaluate test coverage. Specifically, we recommend that the technical assessment document further clarify:

- the ramifications (to coverage) of choosing a "yes" versus "no" response to each question;
- there is seemingly no "middle ground" between "proprietary" and "non-proprietary" and whether clinical utility/clinical validity have already been established in the literature. The answer is almost always somewhere in between.

**ICD-10 Codes**
The ICD-10 diagnosis codes may not always be granular enough to accurately distinguish relapsed, refractory, and/or recurrent cancers as compared to the initial pre-treatment diagnosis code. We recommend the addition of all diagnosis codes that distinguish these cancers for solid tumors.

Thank you again for the opportunity to review and comment on this proposed policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Senior Director of Public Policy, 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