LUNGEVITY
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January 17, 2018

Tamara Syrek Jensen, JD
Director, Coverage & Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
Mailstop S3-02-01
7500 Security Blvd
Baltimore, MD 21244

Dear Ms. Syrek Jensen,

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the 222,500 Americans diagnosed with lung cancer each year and the 527,228 Americans living with the disease, we appreciate the opportunity to submit our comments in response to the "Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)" issued on November 30, 2017.

As a leading patient advocacy group that represents the voice and interest of the national lung cancer survivor community by accelerating research to patients that is meaningful to them, empowering patients to be active participants in their care and care decisions, and helping remove barriers to access to high quality care, LUNGevity applauds the Centers for Medicare & Medicaid Services (CMS) for proposing nationwide coverage for certain NGS tests for advanced cancer, including the FoundationOne CDx test, in this era of unprecedented scientific advancements in the diagnosis and treatment of lung cancer, particularly in the field of biomarker testing. Additionally, we applaud CMS and the Food and Drug Administration (FDA) for their joint efforts in the parallel review program, ensuring that patients receive timely access to FDA-approved products. While we applaud CMS for recognizing the importance of the NGS testing platform and the value of patients receiving high-quality tests to ensure optimal benefits in the proposed national coverage determination (NCD), we believe that a number of urgent concerns must be addressed prior to its finalization: lifetime limits on testing; coverage with evidence development (CED) clarification/modification, and patient access to liquid biopsy NGS testing. We have expanded on these concerns below.

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, diagnosed in about 85 percent of people with lung cancer.[1,2] The complex nature of this disease requires personalized management plans for patients.[2] Since the discovery of the first epidermal growth factor receptor (EGFR) mutation in lung cancer in 2004, targeted therapies have become a major component of the treatment arsenal of NSCLC patients.[3-5] Now at least 10 driver mutations in adenocarcinoma have been identified (EGFR, ALK, ROS, RET, ERB2/HER2 mutations,

ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, KRAS).[6,7] In concert with the identification of an increasing number of targetable mutations is the development of novel, potent, and specifically targeted therapies. Currently, FDA-approved drugs for four mutations (EGFR, ALK, ROS1, and BRAF) are already in clinical practice, and several targeted therapies specific to other mutations are in clinical development.[8] Access to high-quality, timely NGS testing is instrumental for matching patients to the appropriate targeted therapy and advancing precision medicine.

To ensure patient access to high-quality NGS testing and to ensure optimal benefits, we urge CMS to address the following concerns prior to finalization of the NCD:

- **Lifetime Limits Impede Access Based on Outdated Science**

  The draft NCD currently requires that patients have "not been previously testing using the same NGS test." However, new evidence clearly establishes the value of multiple NGS tests in the duration of a patient's treatment journey. An NGS panel at the time of diagnosis and subsequent NGS panels at progression on first- and subsequent lines of therapy fulfill similar and unique purposes.

  As against the traditional sequential testing algorithm for EGFR followed by ALK, an NGS panel at the time of diagnosis simultaneously checks for multiple clinically actionable mutations that help guide physicians to targeted therapies to treat NSCLC.[12] This, in turn, helps timely matching of the patient to the right targeted therapy should a targetable mutation be present. The National Comprehensive Cancer Network (NCCN) guidelines recommend multiplex testing such as NGS platforms for making treatment decisions.[13] An NGS panel at the time of progression helps identify mechanisms of resistance or tumor heterogeneity after treatment with a targeted agent, often independent of the original driver mutation detected at the time of diagnosis. In the recent FLAURA trial of first-line osimertinib in EGFR-positive NSCLC, NGS assays at the time of progression helped identify additional mechanisms of resistance such as mutations in the PIK3CA and the MET genes.[14,15] Currently, drugs targeting the PIK3CA and the MET genes are in clinical development, suggesting that an NGS panel is ideal for determining the next line of treatment for an NSCLC patient who has progressed on a targeted agent.

  As stated above, new mutations in NSCLC are being discovered very quickly and limiting access to one test per a patient's lifetime may be detrimental to their treatment and could prevent their physicians from not only identifying the accurate first-line targeted therapy that may save their life, but also impede access to subsequent lines of therapy.

One of the crucial benefits of NGS testing is allowing a complete profile of the patient's response to prior and post-therapy, and allowing novel classes of drugs to be offered to the patient as their tumor evolves. Offering an NGS panel at the time of diagnosis and at recurrence allows for identifying driver mutations that have drugs in clinical development, thereby allowing patients to be enrolled rapidly in clinical trials. This is especially crucial since NCCN guidelines suggest that clinical trials may often offer the best treatment option in first- and subsequent-line settings. [13]

- **The NCD's Coverage With Evidence Development Requires Further Clarification**

The criterion for CED in the NCD is not well defined and does not indicate an endpoint that can be easily captured by treating physicians, how CMS intends to evaluate the data, or how the data may contribute to a future decision. We appreciate the importance of post-market data in providing valuable evidence of clinical utility; however, CMS must ensure that there are clearly defined guidelines and endpoints so the data collected from patients provides value. Further guidance is also needed on the process for CED, including patient consent, data collection, and who is responsible for the registry.

Additionally, CMS must ensure that the CED process is not overly onerous for patients and physicians, so as to provide a disincentive for participation in the important process that can ultimately bring broader access to testing options. The CED stipulates the use of standard clinical trial endpoints such as Progression Free Survival, Overall Survival, and Objective Response Rate (as determined using RECIST criteria) for evidence development. While we understand that RECIST criteria are standardized metrics used to evaluate clinical trials, the use of these criteria may impede uptake of NGS platforms especially in the community setting, where 80 percent of lung cancer care is delivered in the US[16] and physicians do not routinely use RECIST criteria to evaluate efficacy of treatment. Furthermore, RECIST criteria may not be relevant in certain subsets of NSCLC such as EGFR-positive NSCLC, which grow slowly and continue to respond to EGFR inhibitors even after progression.[17] Instead, we recommend the use of surrogate real-world endpoints such as time-to-treatment failure or treatment change with a proper documentation of reasoning behind treatment failure/change (was the treatment changed due to toxicity or efficacy?).[18] Including such real-world endpoints in the CED will not impose an undue financial burden on patients, physicians, labs, and manufacturers and incentivize adoption, data collection, or participation thereby driving innovation. As proposed, CMS appears to require extensive and burdensome CED even in common circumstances where the patient is not going to receive an on- or off-label targeted therapy, but rather a long-familiar chemotherapy because they had no druggable target.

We suggest that CMS bring together a broad group of stakeholders, including but not limited to, health care providers, pathologist, patients, and patient advocacy groups, to

inform the definition of appropriate criteria for the CED section before finalizing this section of the NCD. Additionally, we encourage CMS to consider the evaluation of well-qualified entities other than the FDA (e.g., the New York State Department of Health) when deciding whether adequate data exists to support the analytic validity, clinical validity, and/or clinical utility of a particular NGS test.

- **The NCD Precludes Patient Access to Covered Liquid Biopsy NGS Testing**

  The utility of liquid biopsies in the clinical management of lung cancer is unquestionable, because as many as 1 out of 4 NCSLC patients may be ineligible for a solid tissue biopsy.[9] In her ASCO 2017 presentation on biomarker testing for lung cancer, LUNGevity Scientific Advisory Board member, Dr. Alice Shaw from Massachusetts General Hospital, pointed out that liquid biopsies may help in (1) initial detection of targetable mutations in advanced-stage NSCLC at the time of diagnosis, (2) identification of acquired resistance mutations and mechanisms of tumor heterogeneity in patients who have relapsed on targeted therapies, and (3) monitoring response to targeted therapies and predicting outcome in advanced-stage NSCLC patients.[10]

  At present, there are no FDA-approved liquid biopsy NGS tests. The draft NCD only proposes to cover such tests under extremely limited circumstances (e.g., if offered within the context of an NIH-NCI National Clinical Trial Network clinical trial). In contrast, a proposed Palmetto MolDX local coverage determination (LCD), which was proposed after careful consideration of the supporting data, would give many Medicare patients with NSCLC access to liquid biopsy NGS tests.[11] This access would effectively be eliminated if this draft NCD's CED and non-coverage sections are finalized as proposed.

  We urge CMS not to preempt proposed local coverage determinations that would provide access to high-quality, lifesaving testing options for patients. The LCDs represent extensive and thorough review, public comment, and careful decision processes. Instead, CMS should consider the data submitted to the Medicare Administrative Contractors (MACs) in support of the local coverage determinations for inclusion in the NCD or provide an additional opportunity for clinical laboratories and manufacturers to provide supporting evidence before determining such tests as non-covered under the final NCD.

LUNGevity is grateful for the opportunity to comment on the "Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)" and is eager to work with CMS and FDA to continue to ensure that patients have timely access to high-quality biomarker testing. In addition, we encourage CMS to help foster an environment of innovation, which could include allowing covered access to laboratory

developed tests that are the subject of favorable final or proposed LCDs while evidence development occurs for FDA approval/clearance.

Once again, we appreciate CMS' attention to and proposed national coverage determination for this important testing platform for lung cancer patients; however, we encourage CMS to consider the areas highlighted above that could benefit from changes and additional clarification.

The recommendations outlined above can be discussed with my staff, myself, and LUNGevity's Scientific Advisory Board, which is made up of some of the world's leading experts in lung cancer biology, practice management, access to innovative medicines, and overall patient care. I can be reached at 240-454-3100 or aeferris@lungevity.org if you have any questions or would like to engage in further dialogue.

Thank you for your attention to this very important matter.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGevity Foundation

ABOUT LUNGEVITY:

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their care and care decisions; and (3) to help remove barriers to access to high quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand, and address unmet patient needs. We also have a world class Scientific Advisory Board that guides the programs and initiatives of the organization. Additionally, we collaborate with other lung cancer patient advocacy groups and organizations, such as the American Lung Association and CHEST, who serve the lung cancer community.

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