November 27, 2019

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

Re: Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

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 approximately 230,000 Americans diagnosed with lung cancer each year and the 538,243 Americans living with the disease,[1] 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-00450R) that was issued on October 29, 2019.

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 providing nationwide coverage for certain NGS tests for advanced cancer through the National Coverage Determination (NCD). While the NCD has provided access to NGS for many lung cancer patients, the rapid pace of evolution of both diagnostics and therapeutics needs to be taken into account as CMS continues to evaluate the utility of NGS for advanced-stage lung cancer. In response to this most recent Proposed Decision Memo, we would like to offer comments on the following four areas:

1. Concerns about CMS' interpretation of the NCD to non-cover NGS for patients with early stage cancers and/or when patients have a personal history of cancer.
2. Concerns about the "not previously been tested using NGS" limitation.
3. Support the proposal to preserve Medicare Administrative Contractor (MAC) discretion to cover germline testing for patients with lung cancer.
4. Request CMS to expand the scope of the existing NCD to cover multiple somatic tests for a single primary cancer during a patient's lifetime, to ensure accurate identification of targetable mutations at diagnosis and at recurrence or progression.

Biomarker testing, typically through comprehensive genomic profiling (such as NGS) and testing for protein markers (such as PD-L1 for immunotherapy), is the first step to accessing personalized medicine. Timely access to diagnostics that inform treatment decisions is critical for all patients, especially cancer patients. In this era of unprecedented scientific advancements for the treatment of lung cancer, lung cancer patients diagnosed today have the advantage, opportunity, and right to learn about the unique biomarker profile of their cancer to help them identify the most appropriate treatment option. Our comments provided below reiterate our stand on the importance of access to timely biomarker testing, through tests such as NGS.

1. **Concerns about CMS' interpretation of the NCD to non-cover NGS for patients with early-stage cancers and/or when patients have a personal history of cancer.**
   LUNGevity remains concerned about CMS interpreting the NCD to non-cover NGS for patients with early-stage cancers and/or when patients have a personal history of cancer. The proposed new coverage language [in sections B.2 (for ovarian and breast cancer) and D (for other types of cancer, including lung cancer)] only require that the patient have a diagnosis of cancer, with no reference to the stage of the patient's condition—so it would seem that early-stage patients should be covered if the criteria are otherwise met. However, the following and troublesome non-coverage language from the original NCD remains: "Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1 above." We ask that CMS clarify their intent as the language as currently written could lead to non-coverage for patients with early-stage cancers and/or when patients have a personal history of cancer. Specifically, in Section B.1, we ask CMS to add a reference to Section D (referenced above) to clarify that patients need not have advanced lung cancer to obtain coverage.

2. **Concerns about the "not previously been tested using NGS" limitation.**
   The language in the Proposed Decision Memo, as currently drafted, that denies coverage for individuals who have been previously tested will create a situation in which a patient who previously received somatic NGS testing would not subsequently be eligible for germline NGS testing. Somatic NGS tests provide different information than germline NGS testing, and many patients will need to receive both types of tests to develop a comprehensive understanding of their individual disease before developing a personalized treatment plan. This may especially impact patients with multiple primary lung cancers (MPLCs). With the advent of low-density computed tomography screening for lung cancer, diagnosis of MPLCs has been on the rise.[2] The genetic heterogeneity across MPLCs impact their treatment.[3] A recent case report suggests that a differential somatic and germline NGS panel may help identify molecular characteristics of MPLC, reiterating the need for flexibility of NGS-based testing in lung cancer.[4] We do not believe the use of restrictive language was the intent of CMS and respectfully request modification of the language to be more inclusive.

3. **Support the proposal to preserve Medicare Administrative Contractor (MAC) discretion to cover germline testing for patients with lung cancer.**
LUNGevity is pleased to see that CMS is proposing to allow MAC discretion regarding germline testing for patients with lung cancer. As we have discussed in previous comments, the science is evolving at an incredibly quick pace, and allowing MAC discretion regarding germline testing for patients with lung cancer offers a degree of flexibility allowing coverage decisions to be made as new evidence is collected without having to undo a National Coverage Determination. While we support this section, we encourage CMS to allow MAC discretion to cover all NGS-based germline tests for cancer patients, patients with suspected/diagnosed hematologic malignancy, and serial minimal residual disease assessments.

   The role of germline mutations in lung cancer development and therapeutic interventions is evolving. The Utah cancer registry, Swedish cancer registry, and Icelandic cancer registry clearly demonstrate an increased risk of developing lung cancer (from 1.9 to 2.7 times) in individuals with a first-degree relative with lung cancer, clearly establishing a hereditary component.[5] In recent years, largely due to our ability to conduct germline sequencing, germline mutations in actionable genes, such as EGFR and HER2, have been detected in lung cancer in non-smokers.[6] One such mutation, EGFR T790M, currently has a matched targeted therapy (osimertinib), suggesting that it is important to include the identification of germline variants as we continue to develop more and more targeted drugs. Furthermore, identification of germline variants associated with lung cancer may help in identifying first-degree relatives who would benefit from cascade testing and subsequent lung cancer screening.[7] Lastly, recent research from Memorial Sloan Kettering Cancer Center demonstrates that parallel tumor sequencing and somatic cell sequencing (to specifically call germline variants) is helpful in identifying tumor-specific variants.[8] Though a single-institution effort, the study reiterates the need to include germline sequencing to further our knowledge and understanding of how these variants behave and their contribution to the development of lung cancer.

4. **Request CMS to expand the scope of the existing NCD to cover multiple somatic tests for a single primary cancer during a patient's lifetime, to ensure accurate identification of targetable mutations at diagnosis and at recurrence or progression.**

   <u>Expanding the one-test-per-lifetime limit for NGS</u>:
   Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, diagnosed in about 85 percent of people with lung cancer.[9-11] The complex nature of this disease requires personalized management plans for patients.[10] 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.[11-14] At present time there are at least 20 somatic driver mutations in NSCLC that have been identified.[15,16] 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 five NSCLC mutations (EGFR, ALK, ROS1, BRAF V600E, and NTRK) are already in clinical practice, and several targeted therapies specific to other mutations are in clinical development.[17,18] Access to high-quality, timely NGS testing (at diagnosis and at recurrence or progression) 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 expand the scope of the existing NCD to cover multiple somatic tests for a single primary cancer during a patient's lifetime in order to ensure accurate identification of targetable mutations at diagnosis and at recurrence or progression.** 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.

NGS at diagnosis: Traditionally, **before a first-line treatment decision** was made for treating lung cancer patients, sequential testing for single mutations was performed. In contrast to 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.[19] 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.[20] Additionally, a multi-analyte testing approach such as NGS is tissue-sparing as against sequential single-analyte testing where each negative result leads to rapid depletion of biopsy tissue. In the case of lung cancer, this is a critical issue because multiple lung biopsies are not feasible for tissue acquisition if tissue is depleted during single-analyte testing.[21,22] The 2018 updated IASLC-CAP-AMP guidelines recommend an NGS-based platform so that tissue is conserved, patients are spared the risk of unnecessary additional biopsies, and small biopsy samples, such as fine needle aspirates, can be tested.[23-25]

NGS at progression or recurrence: It is now well established that tumors evolve with time in response to targeted therapies.[15] These new molecular alterations confer acquired resistance to targeted therapies and are responsible for progression or recurrence after a patient has received first-line targeted treatments. An NGS panel at the time of progression or recurrence helps identify these new 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.[26,27] 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 for a single primary cancer may be detrimental to their treatment and could both prevent their physicians from identifying the accurate first-line targeted therapy that may save their life and impede access to subsequent lines of therapy.

One of the crucial benefits of NGS testing is allowing a complete molecular profile of the patient's tumor before first-line treatment initiation and after treatment(s), 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 or progression also allows for identifying driver mutations that have drugs in clinical development both as first-line treatment options and at progression or recurrence, 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.[20]

LUNGevity is grateful for the opportunity to comment on the Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer and is eager to work with CMS to continue to ensure that patients have timely access to high-quality biomarker testing.

The recommendations outlined above can be discussed with me, my staff, 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 FOUNDATION:

LUNGevity Foundation'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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